Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study

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Summary

Background The combined use of genetic markers and detectable minimal residual disease identifies patients with chronic lymphocytic leukaemia with poor outcome after first-line chemoimmunotherapy. We aimed to assess lenalidomide maintenance therapy in these high-risk patients.

Methods In this randomised, double-blind, phase 3 study (CLLM1; CLL Maintenance 1 of the German CLL Study Group), patients older than 18 years and diagnosed with immunophenotypically confirmed chronic lymphocytic leukaemia with active disease, who responded to chemoimmunotherapy 2–5 months after completion of first-line therapy and who were assessed as having a high risk for an early progression with at least a partial response after four or more cycles of first-line chemoimmunotherapy, were eligible if they had high minimal residual disease levels or intermediate levels combined with an unmutated *IGHV* gene status or *TP53* alterations. Patients were randomly assigned (2:1) to receive either lenalidomide (5 mg) or placebo. Randomisation was done with a fixed block size of three, and was stratified according to the minimal residual disease level achieved after first-line therapy. Maintenance was started with 5 mg daily, and was escalated to the target dose of 15 mg. If tolerated, medication was administered until disease progression. The primary endpoint was progression-free survival according to an independent review. The pre-planned interim analysis done by intention to treat was done after 20% of the calculated progression-free survival events. This study is registered with ClinicalTrials.gov, number NCT01556776; treatment in the lenalidomide group is still ongoing.

Findings Between July 5, 2012, and March 15, 2016, 468 previously untreated patients with chronic lymphocytic leukaemia were screened for the study; 379 (81%) were not eligible. Recruitment was closed prematurely due to poor accrual after 89 of 200 planned patients were randomly assigned: 60 (67%) enrolled patients were assigned to the lenalidomide group and 29 (33%) to the placebo group, of whom 56 (63%) received lenalidomide and 29 (33%) placebo, with a median of 11·0 (IQR 4·5–20·5) treatment cycles at data cutoff. After a median observation time of 17·9 months (IQR 9·1–28·1), the hazard ratio for progression-free survival assessed by an independent review was 0·168 (95% CI 0·074–0·379). Median progression-free survival was 13·3 months (95% CI 9·9–19·7) in the placebo group and not reached (95% CI 32·3–not evaluable) in the lenalidomide group. The most frequent adverse events were skin disorders (35 patients [63%] in the lenalidomide group *vs* eight patients [28%] in the placebo group), gastrointestinal disorders (34 [61%] *vs* eight [28%]), infections (30 [54%] *vs* 19 [66%]), haematological toxicity (28 [50%] *vs* five [17%]), and general disorders (28 [50%] *vs* nine [31%]). One fatal adverse event was reported in each of the treatment groups (one [2%] patient with fatal acute lymphocytic leukaemia in the lenalidomide group and one patient (3%) with fatal multifocal leukoencephalopathy in the placebo group).

Interpretation Lenalidomide is an efficacious maintenance therapy reducing the relative risk of progression in first-line patients with chronic lymphocytic leukaemia who do not achieve minimal residual disease negative disease state following chemoimmunotherapy approaches. The toxicity seems to be acceptable considering the poor prognosis of the eligible patients. The trial independently confirms the clinical significance of a novel, minimal residual disease-based algorithm to predict short progression-free survival, which might be incorporated in future clinical trials to identify candidates for additional maintenance treatment.

Funding Celgene Corporation.

Introduction

The clinical course of chronic lymphocytic leukaemia is highly variable and can be predicted by use of various criteria.[1] Recently, an international prognostic index (CLL-IPI) has been introduced,[2] developed, and refined on the basis of a comprehensive prognostic system.[3] Age, clinical stage, *TP53* alterations, β2 microglobulin, and mutations of the immunoglobulin heavy variable chain

Lancet Haematol 2017

Published Online
September 12, 2017
http://dx.doi.org/10.1016/S2352-3026(17)30171-0

See Online/Comment
http://dx.doi.org/10.1016/S2352-3026(17)30178-3

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Research in context

Evidence before this study

We searched ClinicalTrials.gov and PubMed from August, 2008, up to February, 2017, for reports with the search terms "chronic lymphocytic leukaemia (CLL)", "maintenance", and "lenalidomide" without date or language restrictions. In addition to our study, CLLM1, another randomised phase 3 trial, the CONTINUUM Trial, is listed in ClinicalTrials.gov, which was designed for patients with relapsed chronic lymphocytic leukaemia, but has not been fully published so far. Seven phase 2 studies were listed, three of them without enrolment or early termination because of unsuccessful recruitment. Results of three phase 2 studies, two in the relapsed setting and one after reduced first-line chemoimmunotherapy, have been published recently.

Added value of this study

To the best of our knowledge, the CLLM1 study is the first randomised trial reporting on the value of maintenance therapy with lenalidomide in patients with high-risk chronic lymphocytic leukaemia after first-line therapy. The results from the study show that lenalidomide is highly effective in delaying disease progression.

Implications of all the available evidence

As there are currently rapid therapeutic advances for patients with chronic lymphocytic leukaemia, including kinase or BCL2 inhibitors, the results of this study are unlikely to affect the current first-line therapy for chronic lymphocytic leukaemia. However, lenalidomide might be considered in selected high-risk patients where first-line therapy does not achieve a deep minimal residual disease negative remission of chronic lymphocytic leukaemia or where inhibitors are not available. The trial independently confirms the clinical significance of a novel, minimal residual disease-based algorithm to predict short progression-free survival, which might be incorporated in future clinical trials to identify candidates for additional maintenance treatment.

(*IGHV*) gene were identified as independent prognostic factors for overall survival in patients treated with chemoimmunotherapy.

As previously published,[4] a combination of high minimal residual disease levels of 10^{-2} (1 in 100 cells) or higher or a combination of intermediate minimal residual disease levels of 10^{-4} to less than 10^{-2} plus at least one of the three parameters (del[17p] or *TP53* mutation or an unmutated *IGHV*-status) defined patients at high risk of early disease progression. The minimal residual disease levels achieved with various therapies predicted the duration of progression-free survival and treatment-free survival, as well as overall survival,[5–9] and represent an independent prognostic factor irrespective of type or line of therapy.[10] There is increasing evidence to support the use of minimal residual disease assessment as a surrogate endpoint in clinical trials and it has been recently approved by the European Medicines Agency as an intermediate endpoint in prospective studies of chronic lymphocytic leukaemia.[11]

In the past decade, impressive progress has been achieved in the management of chronic lymphocytic leukaemia. Monoclonal antibodies combined with purine analogues, alkylating drugs, or use of both have improved the proportion of patients achieving a clinical response and prolonged progression-free survival.[12–15] In addition, new treatment options with small molecules, such as kinase inhibitors and BCL2 inhibitors,[16] significantly broadened the range of treatment options.

The CLLM1 study was planned for patients who respond poorly to intensive first-line therapy (eg, fludarabine, cyclophosphamide, and rituximab or fludarabine, cyclophosphamide, and rituximab-like regimen). These patients traditionally experienced early progression, and salvage therapies are not sufficiently effective,[17] which leads to a significantly reduced overall survival. Thus, they should be considered as patients with high-risk chronic lymphocytic leukaemia and eligible for maintenance strategies.[18]

Lenalidomide, a 4-amino-glutamyl analogue of thalidomide, has shown significant clinical activity in chronic lymphocytic leukaemia.[19] Because of its multifaceted mechanism of action with effects on chronic lymphocytic leukaemia cells itself, including cereblon-mediated antiproliferative activity but also immunomodulatory effects leading to an improved immunosurveillance,[20,21] lenalidomide has been considered promising in this setting. We aimed to assess lenalidomide maintenance therapy in these high-risk patients.

Methods

Study design and participants

CLLM1 is a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study done at 62 centres across five countries (Austria, Germany, Italy, the Netherlands, and Spain; appendix p 14). Patients were pre-screened before the start of the first-line treatment; baseline status and cytogenetic characteristics were documented. Screening was started after the first-line treatment; response to treatment was evaluated, and minimal residual disease levels in the peripheral blood were assessed centrally. Patients older than 18 years and diagnosed with immunophenotypically confirmed chronic lymphocytic leukaemia with active disease, who responded to chemoimmunotherapy 2–5 months after completion of first-line therapy and who were assessed as having a high risk for an early progression, defined by minimal residual disease levels of 10^{-2} or higher or

minimal residual disease levels of 10^{-4} to less than 10^{-2} after completion of first-line treatment combined with either an unmutated *IGHV* gene status, del(17p) or *TP53* mutation at baseline, were eligible. Additional inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, physical fitness as defined by a cumulative illness rating scale (CIRS)[22] not greater than 6, and a creatinine clearance of 70 mL/min or higher (appendix pp 2–3). Major exclusion criteria were high burden of comorbidities, resulting in a CIRS score of more than 6, less than four cycles of chemoimmunotherapy, and non-responders to first-line treatment (full inclusion and exclusion criteria are listed in the appendix pp 2–3).

This study was done according to the Declaration of Helsinki. The leading ethics committee that approvied the study was the ethics committee of the University of Cologne, in agreement with 26 involved ethics committees in Germany. For the other countries there was also one leading ethics committee (ethics committee Vienna for Austria, ethics committee Amsterdam for the Netherlands, ethics committee Milan for Italy, and ethics committee Barcelona for Spain) but the study was submitted according to country-specific law to all involved ethics committees as well. Each patient provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned (2:1) to receive either lenalidomide or placebo using an electronic web/voicemail randomisation system (IWRS) with a secure, password-protected database on the basis of a computer-generated randomisation schedule prepared by ICON (Dublin, Ireland). Neither the sponsor nor the investigators had access to the randomisation schedule. The randomisation was balanced by the use of a fixed block size of three. Stratification was done according to the minimal residual disease level (intermediate or high) at timepoint of randomisation. Patient randomisation confirmation including a unique treatment code was sent automatically by the IWRS to the investigators. Thus, patient allocation was achieved independently from the study investigators. Investigators, patients, study personal, and sponsor were all masked to the actual treatment; capsules that were identical in appearance were provided.

Procedures

Study treatment consisted of lenalidomide or placebo starting with 5 mg daily in the first 28 day cycle following previous experience in a consolidation trial.[23] If the 5 mg dose level was well tolerated, dose was escalated to 10 mg daily in each 28 day cycle in cycles 2 to 6; the target dose of 15 mg daily was given starting with the seventh cycle up to progression of disease. Further escalations (to 20 mg starting with the 13th cycle and to 25 mg starting with the 19th cycle, respectively) were guided by minimal residual disease assessments and were allowed in patients with minimal residual disease levels of 10^{-4} or higher in peripheral blood that tolerated previous dose levels. 25 mg was the maximal daily dose of lenalidomide. If patients experienced adverse events, dose interruptions, reductions, discontinuations, and re-escalations were done according to the guidelines in the protocol. Patients who did not tolerate the de-escalated dose of 2·5 mg every other day for at least 28 days or patients with treatment interruptions at any dose level for more than 35 days had to discontinue the maintenance treatment. Patients were followed for progression monthly, and minimal residual disease assessments were done in all patients still in remission every 6 months. According to their risk for thromboembolic events, patients received either low dose aspirin daily, or appropriate anti-coagulation prophylactic therapies.

See Online for appendix

Confirmation of diagnosis by immunophenotyping was done centrally or in local labs. To assess whether the criteria for high risk were met, minimal residual disease assessment in the peripheral blood was done centrally by four-colour flow cytometry according to previously published procedures following European Research Initiative on Chronic Lymphocytic Leukemia guidelines.[24,25] Analyses of genomic aberrations by fluorescent in-situ hybridisation (FISH) and *IGHV*/*TP53* mutation status by DNA sequencing were done either in the central reference laboratories or in local laboratories. Clinical disease assessments were completed before first-line therapy and repeated at screening and 3 monthly until end of study, including tumour assessments, chemistry, CIRS, and ECOG performance status. CT scans were done at screening and repeated if clinically indicated after 12 cycles and at progression of disease. Responses and disease progression were classified according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL)-guidelines,[26] assessed by both the central independent review committee and the investigators. Adverse events were documented according to the Common Terminology Criteria (CTC) for Adverse Events version 4. Adverse events have to be reported with the start of treatment and up to 28 days after discontinuation of the study treatment; serious adverse events have to be reported indefinitely.

Outcomes

The primary endpoint of this study was progression-free survival based on the assessment of an independent review committee, defined as the time between randomisation and the first date of documented disease progression or death from any cause. Secondary endpoints were progression-free survival based on the investigator's assessment, progression-free survival based on the investigator's assessment censoring patients who started new anti-leukaemic therapy before disease progression, overall survival (defined as the time between randomisation and death from any cause), safety parameters, evaluation of minimal residual disease levels at different timepoints, health-related quality of life

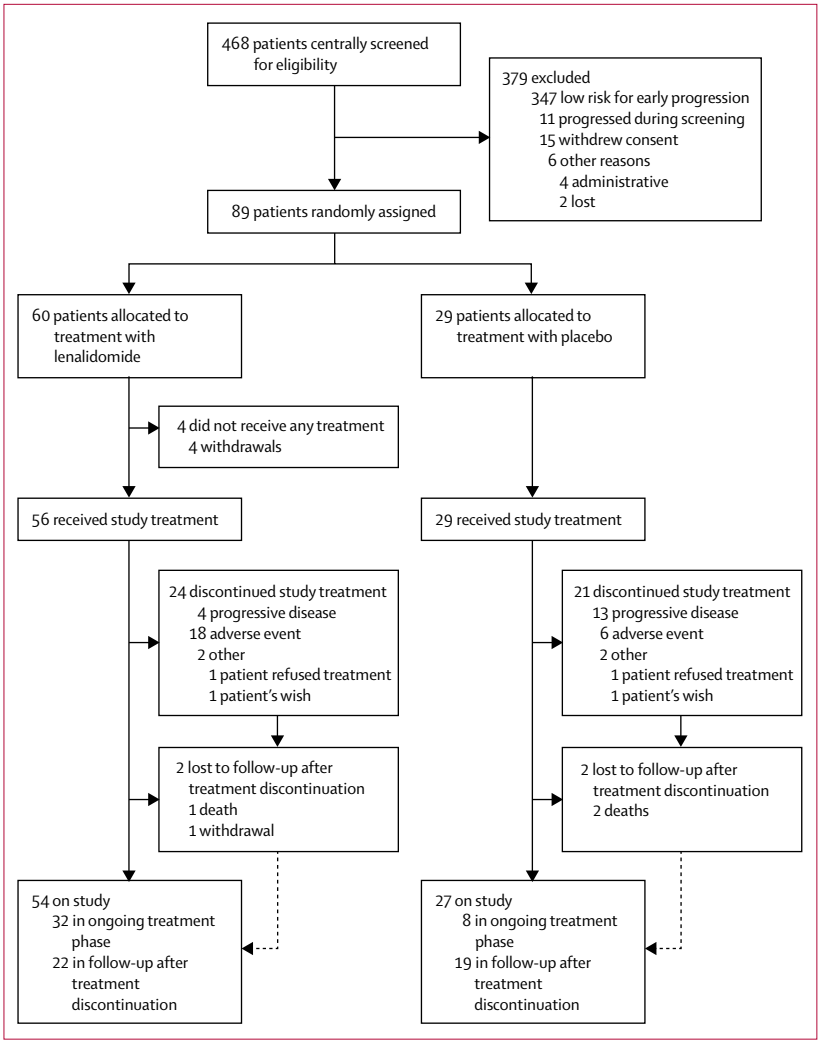

Figure 1: **Trial profile**

	Lenalidomide (n=60)	Placebo (n=29)
Age		
Median (IQR)	64 (57·3–69·8)	64 (58·0–69·5)
>65 years	27 (45%)	14 (48%)
>70 years	13 (22%)	6 (21%)
Sex		
Female	7 (12%)	6 (21%)
Male	53 (88%)	23 (79%)
Cumulative illness rating scale (CIRS) score	2 (0–4)	2 (0–4)
Creatinine clearance (mL/min)	91·5 (76·0–114·3)	95·1 (80·7–115·5)
Minimal residual disease level at randomisation		
$\geq 10^{-2}$	23 (38%)	12 (41%)
$\geq 10^{-4}$ to $<10^{-2}$	37 (62%)	17 (59%)
Cytogenetic abnormalities*	n=52	n=26
del(17p)	7 (14%)	2 (8%)
del(11q)	16 (31%)	7 (27%)
trisomy 12	3 (6%)	6 (23%)
No abnormalities	18 (35%)	5 (19%)
Sole del(13q)	8 (15%)	6 (23%)
Other aberrations		
TP53 mutational status (n=83)	10 (18%)/56	7 (26%)/27
IGHV unmutated (n=81)	50 (91%)/55	24 (92%)/26
Complex karyotype (n=43)	5 (17%)/29	4 (29%)/14
Type of first-line treatment		
Fludarabine, cyclophosphamide, rituximab	22 (37%)	12 (41%)
Bendamustine plus rituximab	37 (62%)	17 (59%)
Fludarabine plus cyclophosphamide	1 (2%)	0
Response to first-line treatment	n=60	n=29
Complete remission	5 (8%)	2 (7%)
Complete remission with incomplete bone marrow recovery	2 (3%)	1 (3%)
Clinical complete remission	13 (22%)	9 (31%)
Clinical complete remission with incomplete bone marrow recovery	2 (3%)	1 (3%)
Partial remission	38 (63%)	16 (55%)

Data are median (IQR) or n (%). *Cytogenetic abnormalities according to hierarchical model (according to Döhner et al).[27]

Table 1: **Patient demographics and baseline characteristics**

analysis by the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-c30) and the EuroQol-5 dimension s questionnaire (EQ-5D), time to next treatment (defined as the time between randomisation and the start of the first subsequent treatment for chronic lymphocytic leukaemia), event-free survival (defined as the time between randomisation to the date of first documented disease progression [as defined by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) response criteria and estimated by the independent review committee], the start of the first subsequent treatment for chronic lymphocytic leukaemia, or death by any cause), and treatment-free survival after second-line treatment (defined as the time between the start of the first subsequent treatment and the second subsequent treatment for chronic lymphocytic leukaemia or death by any cause). This report includes the final results of the primary efficacy analysis, safety aspects, and results of major secondary endpoints, including progression-free survival based on the investigator's assessment, event-free survival, time to next treatment, overall survival, and minimal residual disease levels. Analyses regarding health-related quality of life and treatment-free survival after second-line treatment were not part of this analysis and will be done and presented later. Because there were no patients who started new anti-leukaemic therapy before disease progression, the secondary endpoint progression-free survival based on the investigator's assessment censoring patients who started new anti-

	Lenalidomide (n=60)	Placebo (n=29)	HR (95% CI); p value
Primary endpoint (progression-free survival)			
Median (95% CI), months	NR (32·3–NE)	13·3 (9·9–19·7)	
12 month (95% CI)	89·7% (80·9–98·4)	56·9% (37·1–76·7)	..
24 month (95% CI)	76·5% (62·4–90·6)	24·8% (5·5–44·1)	..
Secondary endpoints			
Time-to-event endpoints			
Progression-free survival according to the assessment of an independent review committee based on the per-protocol population	..	..	0·160* (0·067–0·380) <0·0001
Median (95% CI), months	NR (32·3–NE)	13·3 (9·9–19·5)	..
12 month (95% CI)	89·0% (79·8–98·2)	56·6% (35·8–77·4)	..
24 month (95% CI)	78·9% (65·3–92·5)	21·2% (1·8–40·7)	..
Progression-free survival based on the investigator's assessment	..		0·231 (0·104–0·511); <0·0001
Median (95% CI), months	NR (32·3–NE)	14·6 (10·8–28·5)	..
12 month (95% CI)	88·6% (79·0–98·1)	59·3% (39·6–79·3)	..
24 month (95% CI)	74·9% (60·1–89·8)	36·4% (14·8–58·0)	..
Event-free survival	..		0·184 (0·084–0·402); <0·0001
Median (95% CI), months	NR (32·3–NE)	13·3 (9·9–19·4)	..
12 month (95% CI)	89·9% (81·4–98·4)	56·9% (37·1–76·7)	..
24 month (95% CI)	76·9% (63·0–90·8)	25·0% (5·7–44·4)	..
Time to next treatment	..		0·397 (0·105–0·837); 0·015
Median (95% CI), months	NR (NE)	29·0 (17·1–NE)	..
12 month (95% CI)	93·3% (85·8–100·0)	96·4% (89·6–100·0)	..
24 month (95% CI)	85·9% (74·0–97·9)	55·1% (30·6–79·6)	..
Overall survival	..		0·266 (0·024–2·931); 0·245
Median (95% CI), months	NR (NE)	NR (NE)	
12 month (95% CI)	100·0% (100·0–100·0)	92·4% (82·4–100·0)	..
24 month (95% CI)	96·7% (90·2–100·0)	92·4% (82·4–100·0)	..
Minimal residual disease			
Status at cycle 7 (n=53)	(n=39)	(n=14)	..
Negative	3 (8%)	0	..
Intermediate	20 (51%)	6 (43%)	..
Positive	16 (41%)	8 (57%)	..
Status at cycle 12 (n=36)	(n=27)	(n=9)	..
Negative	2 (7%)	0	..
Intermediate	13 (48%)	2 (22%)	..
Positive	12 (44%)	7 (78%)	..

NR=not reached. NE=not evaluable. *Adjusted for minimal residual disease status at randomisation.

Table 2: **Primary and secondary endpoints**

leukaemic therapy before disease progression was not reported separately.

Statistical analysis

The calculation of the sample size of the study was driven by the primary endpoint, progression-free survival. Data published before the initiation of the study[4] indicated that median progression-free survival could be expected at 22·4 months in the placebo group; the intervention was assumed to lead to an improvement of the median progression-free survival by 75%, which should result in a median progression-free survival of 39·2 months and a corresponding hazard ratio of 0·571. 118 progression-free survival events were required to have 80% power at a 5% significance level yielding 200 patients to be recruited. In the course of the study, it was realised that the recruitment goal of 200 patients might not be reached. Therefore, two interim analyses allowing stopping for efficacy or futility (non-binding) after 24 (20%) and 48 (41%) progression-free survival events were implemented subsequently using a group sequential testing design. The corresponding p values for early stopping for futility and efficacy were 0·1889 and 0·0006 as lower and upper boundaries, respectively (further details on the statistical analysis are included in the appendix pp 4–5).

For the primary endpoint analysis, a two-sided stratified log-rank test was done using the minimal residual disease status at randomisation as stratification factor.

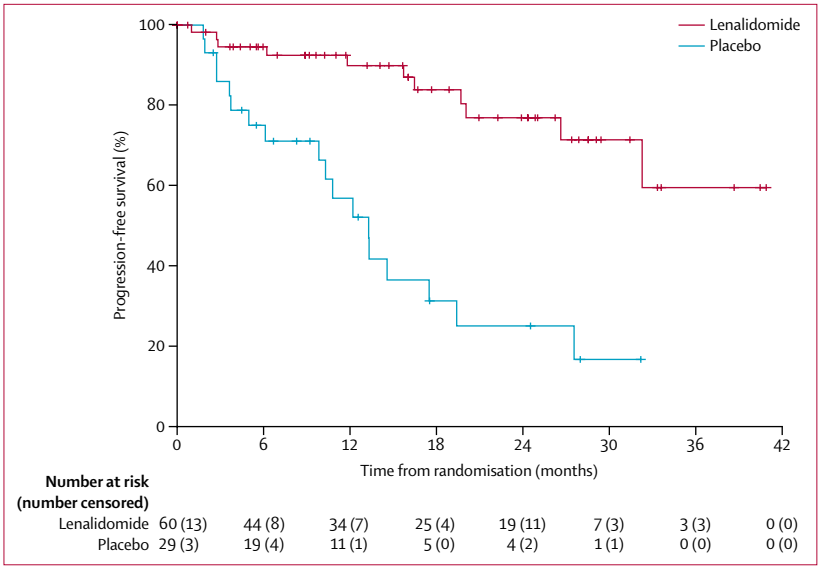

Figure 2: **Primary endpoint—progression-free survival according to independent review**

Progression-free survival was estimated using the Kaplan-Meier method. Estimate of the treatment effect was expressed by the hazard ratio (HR), including the 95% CI adjusted for the minimal residual disease status at randomisation as stratification factor. The calculation was done through a Cox proportional hazard regression model. The assumption of proportional hazards was not verified before the analysis. In terms of sensitivity, the analysis was repeated based on the per-protocol population comprising all randomised participants who had received at least two complete cycles of study treatment unless they had progressed or had died and provided that they fulfilled the inclusion criteria and have no major protocol violations (appendix pp 2–3). Exploratory post-hoc subgroup analyses were done considering the factors minimal residual disease status at randomisation, the type of first-line treatment (including fludarabine, cyclophosphamide plus rituximab; fludarabine, cyclophosphamide and bendamustine plus rituximab), and the presence of *TP53* aberrations. Analyses of secondary time-to-event endpoints and exploratory post-hoc subgroup analyses were done in a similar way as the primary endpoint analysis, including the Kaplan-Meier method and the calculation of HRs including 95% CIs through the Cox proportional hazard regression models. To compare survival curves, two-sided non-stratified log-rank tests were done for secondary time-to-event endpoints. Adjustments for multiple comparisons were not considered for analysing secondary endpoints. Assessments of minimal residual disease levels were analysed at cycle 7 and at cycle 12, respectively. Relative frequencies were calculated based on those patients for whom a sample at cycle 7 and cycle 12 was available. All statistical tests were two sided and a p value of less than 0·05 was considered significant. Results presented in this publication are based on the intention-to-treat (ITT) population. All patients who received at least one dose of study treatment (safety population) were included in the safety analyses. Data were analysed using SPSS version 24.0 and SAS version 9.4.

This study is registered with ClinicalTrials.gov, number NCT01556776.

Role of the funding source

The study was funded by Celgene. The company had no involvement in the design, data collection, data analysis, data interpretation, or writing of the report. The study sponsor was the University of Cologne; the representative of the sponsor for this study was the corresponding author. The study office of the German CLL Study Group was responsible for study design, data collection, data cleaning, and medical review. The corresponding author was responsible for data analysis, data interpretation, and writing of the report and had full access to all the data and the final responsibility to submit for publication.

Results

Between July 5, 2012, and March 15, 2016, 468 previously untreated patients with chronic lymphocytic leukaemia were screened for the study (figure 1). The majority of patients were ineligible for randomisation (347 [74%]) because of minimal residual disease negativity or low risk after first-line treatment. The first pre-planned interim analysis was done based on a dataset with data cut-off date March 31, 2016, by the Data Safety Monitoring Board (DSMB). At this timepoint, 89 patients were randomly assigned; 29 (33%) to receive placebo and 60 (67%) to receive lenalidomide treatment (intention-to-treat [ITT] population). Patient characteristics in the two groups were similar (table 1). Median observation time for the whole ITT population was 17·9 months (IQR 9·1–28·1); 16·7 months (IQR 8·9–28·5) for the lenalidomide group and 19·7 (9·9–29·4) for the placebo group.

Four (7%) patients in the lenalidomide group withdrew consent immediately after randomisation and did not receive any dose of the treatment. 56 (93%) patients started treatment with lenalidomide. Median number of treatment courses administered was 11·5 (IQR 5·0–22·8) in the lenalidomide group compared with 10·0 (4·0–20·0) in the placebo group. Median cumulative doses were 3005·0 mg (IQR 1050·0–6213·8) for lenalidomide and 2575·0 mg (910·0–6499·0) for placebo. Median daily dose was 9·1 mg (IQR 6·3–12·5) for lenalidomide and 9·2 mg (7·9–13·0) for placebo.

56 patients (93%) randomly assigned to lenalidomide received at least one dose of 5 mg daily, 45 (80%) were escalated to 10 mg, 26 (46%) to the target dose of 15 mg, 10 (18%) to 20 mg, and one (2%) to 25 mg daily lenalidomide, respectively. In comparison, all 29 (100%) patients in the placebo group received at least one dose of 5 mg daily, 27 (93%) received 10 mg, 14 (48%) received 15 mg, six (21%) received 20 mg, and four (14%) received 25 mg, respectively.

As of March 31, 2016, 24 (43%) patients with lenalidomide had discontinued treatment. Treatment with lenalidomide significantly improved progression-free survival. Median progression-free survival in the placebo group was 13·3 months (95% CI 9·9–19·7) versus not reached (32·3–not evaluable) in the lenalidomide group (table 2). Progression-free survival at 12 and 24 months is reported in table 2. This translated into a hazard ratio (HR; adjusted for baseline minimal residual disease level) of 0·168 (95% CI 0·074–0·379, p<0·0001; figure 2). Thus, the primary endpoint was successfully met as this p value was below the upper boundary for efficacy (p=0·0006). As the first interim analysis was significant in favour of lenalidomide, robust and reliable with regard to the defined stopping boundaries, the DSMB recommended unmasking the patients and further recruitment was stopped.

The analysis of the per-protocol population (79 patients included; 53 [67%] in the lenalidomide group and 26 [33%] in the placebo group) confirmed the results of the ITT analysis with a median progression-free survival in the placebo group of 13·3 months (95% CI 9·9–19·5) versus not reached (32·3–not evaluable) for lenalidomide (HR 0·160 [95% CI 0·067–0·380] adjusted for minimal residual disease status at randomisation; p<0·0001; table 2, appendix p 6). Similar results were found for investigator-assessed progression-free survival: median progression-free survival in the placebo group was 14·6 months (95% CI 10·8–28·5) versus not reached (32·3–NE) in the lenalidomide group with a hazard ratio of 0·231 (95% CI 0·104–0·511; p<0·0001; table 2, appendix p 8).

Patients were stratified for randomisation according to the baseline minimal residual disease level. The advantage for lenalidomide was noted in both the stratification cohorts (appendix pp 9–10). Patients with an intermediate minimal residual disease level achieved better results with a median progression-free survival of 19·4 months (95% CI 10·1–28·7) for the placebo group and not reached (not evaluable) in the lenalidomide group. The HR was 0·171 (95% CI 0·051–0·571; p=0·0012). Patients with a high minimal residual disease level had a poor outcome with 4·4 months (95% CI 2·8–12·2) in the placebo group versus 32·3 months (15·7–32·3) in the lenalidomide group. The hazard ratio was 0·165 (95% CI 0·055–0·500; p=0·00033). Regarding the first-line treatment chosen, results were similar for patients receiving fludarabine, cyclophosphamide, rituximab or fludarabine plus cyclophosphamide and bendamustine plus rituximab, respectively (appendix pp 11–12). Lenalidomide following fludarabine, cyclophosphamide, rituximab or fludarabine, cyclophosphamide resulted in the proportion of patients acheiving progression-free survival to be 88% (95% CI 73·1–100·0) at 12 months and 69% (41·9–95·6) for 24 months; for lenalidomide following bendamustine plus rituximab first-line, the proportions were 90% (79·1–100·0) at 12 months and 81% (65·7–96·4) at 24 months. Lenalidomide treatment

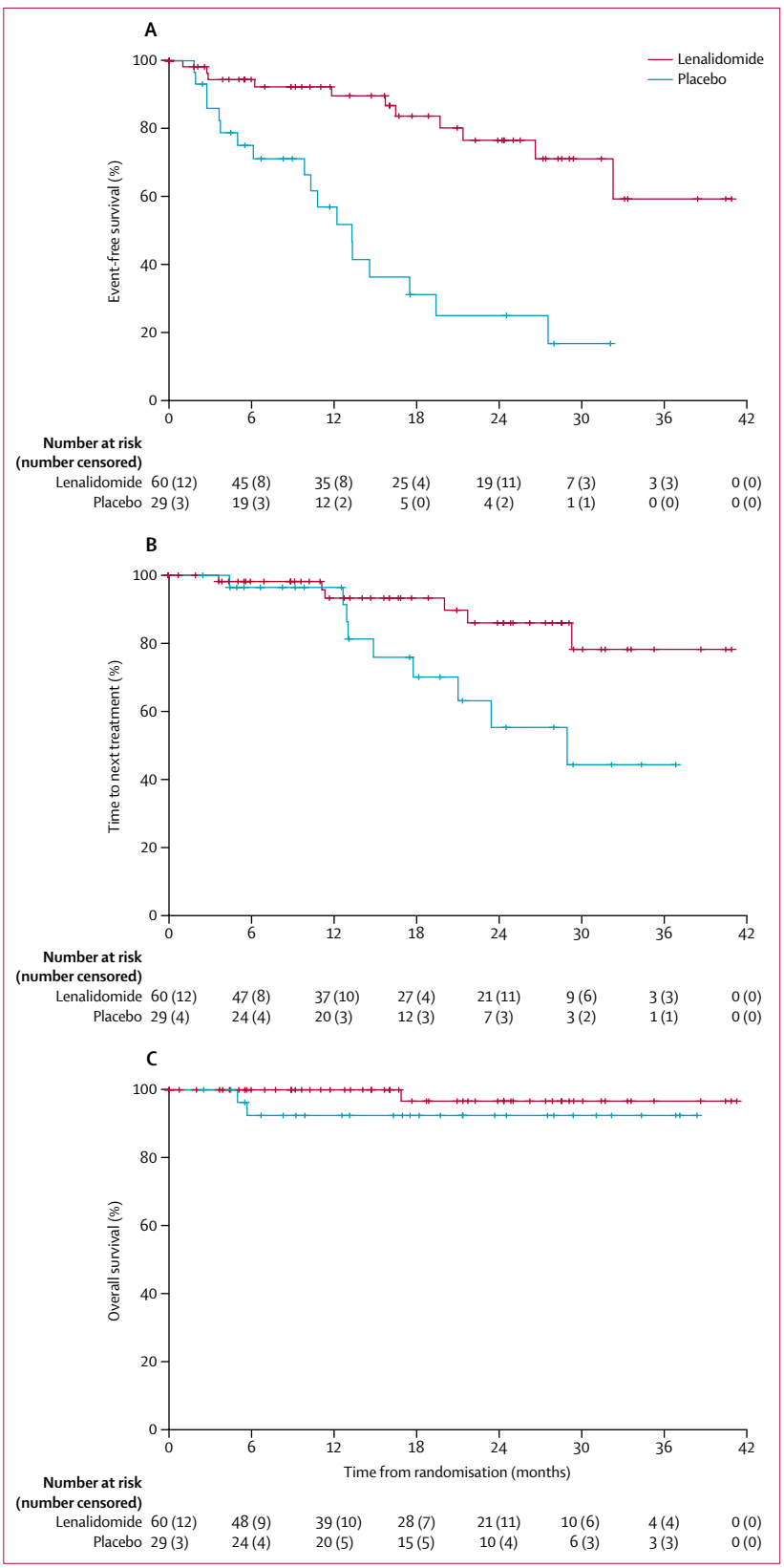

Figure 3: **Secondary endpoints—event-free survival (A), time to next treatment (B), and overall survival (C)**

resulted in a significant benefit for both, patients with and without *TP53* aberrations (appendix pp 13–14). Median event-free survival was 13·3 months (95% CI 9·9–19·4) for the placebo group versus not reached (32·3–not evaluable) in the lenalidomide group (p<0·0001). Median time to next chronic lymphocytic leukaemia treatment was

	Lenalidomide (n=60)				Placebo (n=29)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Patients with adverse events	19 (33%)	24 (43%)	11 (20%)	1 (2%)	16 (55%)	7 (24%)	2 (7%)	1 (3%)
Blood and lymphatic disorders	4 (7%)	14 (25%)	9 (16%)	0	1 (3%)	3 (10%)	1 (3%)	0
Leucopenia	2 (4%)	6 (11%)	1 (2%)	0	1 (3%)	1 (3%)	0	0
Neutropenia	1 (2%)	10 (18%)	9 (16%)	0	0	1 (3%)	1 (3%)	0
Cardiac disorders	5 (9%)	1 (2%)	0	0	0	0	0	0
Coronary artery stenosis	0	1 (2%)	0	0	0	0	0	0
Ear and labyrinth disorders	3 (5%)	0	0	0	2 (7%)	1 (3%)	0	0
Vertigo	1 (2%)	0	0	0	2 (7%)	1 (3%)	0	0
Eye disorders	6 (11%)	0	0	0	2 (7%)	0	0	0
Gastrointestinal disorders	27 (48%)	6 (11%)	1 (2%)	0	8 (28%)	0	0	0
Constipation	11 (20%)	1 (2%)	0	0	2 (7%)	0	0	0
Dental caries	0	1 (2%)	0	0	0	0	0	0
Diarrhoea	16 (29%)	2 (4%)	0	0	2 (7%)	0	0	0
Inguinal hernia	0	1 (2%)	0	0	0	0	0	0
Mechanical ileus	0	0	1 (2%)	0	0	0	0	0
Stomatitis	0	1 (2%)	0	0	1 (3)	0	0	0
General disorders and administration site conditions	23 (41%)	5 (9%)	0	0	9 (31%)	0	0	0
Fatigue	10 (18%)	4 (7%)	0	0	6 (21%)	0	0	0
General physical health deterioration	2 (4%)	1 (2%)	0	0	0	0	0	0
Immune system disorders	0	1 (2%)	0	0	0	0	0	0
Dermatitis allergic	0	1 (2%)	0	0	0	0	0	0
Infections and infestations	22 (39%)	7 (13%)	1 (2%)	0	16 (55%)	1 (3%)	1 (3%)	1 (3%)
Cellutis	0	1 (2%)	0	0	0	0	0	0
Febrile infection	1 (2%)	0	0	0	0	1 (3%)	0	0
Herpes zoster	1 (2%)	1 (2%)	0	0	0	0	0	0
Lower respiratory tract infections*	6 (11%)	3 (5%)	1 (2%)	0	3 (10%)	0	1 (3%)	0
Nasopharyngitis/rhinitis	19 (34%)	0	0	0	9 (31%)	0	0	0
Neutropenic infection	0	1 (2%)	0	0	0	0	0	0
Progressive multifocal leukoencephalopathy	0	0	0	0	0	0	0	1 (3%)
Septic arthritis staphylococcal	0	1 (2%)	0	0	0	0	0	0
Sinusitis	1 (2%)	1 (2%)	0	0	1 (3%)	0	0	0
Upper respiratory tract infection	4 (7%)	0	0	0	2 (7%)	0	0	0
Wound infection staphylococcal	0	1 (2%)	0	0	0	0	0	0
Injury, poisoning, and procedural complications	1 (2%)	2 (4%)	0	0	3 (10%)	0	0	0
Radius fracture	0	1 (2%)	0	0	0	0	0	0
Tendon rupture	0	1 (2%)	0	0	0	0	0	0
Investigations	7 (13%)	1 (2%)	0	0	3 (10%)	0	0	0
Catheterisation cardiac	0	1 (2%)	0	0	0	0	0	0
Metabolism and nutrition disorders	6 (11%)	0	0	0	3 (10%)	0	0	0
Musculoskeletal and connective tissue disorders	20 (36%)	2 (4%)	0	0	8 (28%)	0	0	0
Arthralgia	10 (18%)	0	0	0	1 (3%)	0	0	0
Muscle spasms	7 (13%)	0	0	0	3 (10%)	0	0	0
Rotator cuff syndrome	0	1 (2%)	0	0	0	0	0	0
Spinal column stenosis	0	1 (2%)	0	0	0	0	0	0

(Table 3 continues on next page)

	Lenalidomide (n=60)				Placebo (n=29)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3 (5%)	3 (5%)	0	1 (2%)	1 (3%)	3 (10%)	0	0
Acute lymphocytic leukaemia	0	0	0	1 (2%)	0	0	0	0
Basal cell carcinoma	1 (2%)	1 (2%)	0	0	0	1 (3%)	0	0
Prostate cancer	1 (2%)	0	0	0	0	0	0	0
Squamous cell carcinoma	0	2 (4%)	0	0	0	1 (3%)	0	0
Thyroid adenoma	0	0	0	0	0	1 (3%)	0	0
Nervous system disorders	17 (30%)	3 (5%)	0	0	5 (18%)	0	0	0
Dysaesthesia	0	1 (2%)	0	0	0	0	0	0
Headache	7 (13%)	0	0	0	1 (3%)	0	0	0
Syncope	0	2 (4%)	0	0	1 (3%)	0	0	0
Psychiatric disorders	8 (14%)	1 (2%)	0	0	0	0	0	0
Agitation	0	1 (2%)	0	0	0	0	0	0
Renal and urinary disorders	2 (4%)	1 (2%)	0	0	0	1 (3%)	0	0
Acute kidney injury	0	0	0	0	0	1 (3%)	0	0
Glomerulonephritis minimal lesion	0	1 (2%)	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	20 (36%)	1 (2%)	1 (2%)	0	4 (14%)	0	0	0
Cough	10 (18%)	0	0	0	3 (10%)	0	0	0
Dyspnoea	5 (9%)	1 (2%)	0	0	1 (3%)	0	0	0
Pulmonary embolism	0	0	1 (2%)	0	0	0	0	0
Skin and subcutaneous tissue disorders	33 (59%)	2 (4%)	0	0	8 (28%)	0	0	0
Pruritus	7 (13%)	0	0	0	2 (7%)	0	0	0
Rash	14 (25%)	2 (4%)	0	0	2 (7%)	0	0	0
Vascular disorders	5 (9%)	2 (4%)	0	0	4 (14%)	1 (3%)	0	0
Deep vein thrombosis	1 (2%)	1 (2%)	0	0	0	0	0	0
Thrombosis	0	1 (2%)	0	0	0	0	0	0

Events listed are treatment-emergent adverse events including all grade 3–5 adverse events regardless of frequency and adverse events of any grade occurring in at least 10% of the patients in either treatment group. CTC=Common Terminology Criteria for Adverse Events version 4. *Includes bronchitis, bronchopneumonia, bronchopulmonary aspergillosis, *Pneumocystis Jirovecii* pneumonia, pneumonia, pseudomonas bronchitis, and pulmonary sepsis.

***Table 3*: Incidence of CTC adverse events according to treatment group**

29·0 months (95% CI 17·1–not evaluable) in the placebo group versus not reached (not evaluable) in the lenalidomide group (p=0·015; figure 3A, B; table 2). At time of data cutoff, only three events (one in the lenalidomide group and two in the placebo group) for overall survival were documented. No significant difference was noted between the two treatment groups for overall survival (HR 0·266 [95% CI 0·024–2·931]; p=0·245; figure 3C; table 2).

By design, all patients had detectable minimal residual disease at the timepoint of randomisation. Intermediate and high minimal residual disease levels were reported in 37 (62%) and 23 (38%) patients of the lenalidomide and in 17 (59%) and 12 (41%) patients of the placebo group, respectively. Because the final patient was randomised only 2 months before data cutoff, a reasonable number of samples were not available for further planned timepoints so far. 53 samples (39 [74%] for patients in the lenalidomide group and 14 [26%] for patients in the placebo group) could be analysed at cycle 7 and 36 samples (27 [75%] for patients in the lenalidomide group and nine [25%] for patients in the placebo group) could be analysed at cycle 12. However, the analysis of the samples received showed that whereas in the placebo group the proportion of patients with a high minimal residual disease level increased over time to 57% (eight of 14 patients) at cycle 7 and 78% (seven of nine patients) at cycle 12, this increase was reduced in the lenalidomide group with 41% (16 of 39 patients) after cycle 7 and 44% (12 of 27 patients) after cycle 12. Conversion to minimal residual disease negativity was observed in three (8%) of the patients after cycle 7 and two (7%) after cycle 12 in the lenalidomide group, and was not observed in the placebo group.

The safety population included all patients with at least one dose of study drug (56 patients in the lenalidomide group and 29 patients in the placebo group). Adverse events of any grade were reported for 55 (98%) patients in the lenalidomide group and 26 (90%) patients in the placebo group (table 3). Grade 3 or 4 events were observed in 35 (63%) patients in the lenalidomide group

and in nine (31%) patients in the placebo group. One adverse event-related death was reported in each of the treatment groups (one [2%] patient with fatal acute lymphocytic leukaemia in the lenalidomide group and one patient (3%) with fatal multifocal leukoencephalopathy in the placebo group).

Skin disorders were the most frequent events in the lenalidomide group in 35 (63%) of the patients (16 [29%] with rash, seven [13%] with pruritus) compared with eight (28%) of the patients in the placebo group (two [7%] with rash and two [7%] with pruritus).

Gastrointestinal disorders were reported for 34 (61%) of the patients (12 [21%] with constipation and 18 [33%] with diarrhoea) in the lenalidomide group and for eight (28%) of the patients in the placebo group (two [7%] with constipation and two [7%] with diarrhoea). Infections occurred in 30 (54%) of the patients in the lenalidomide group, ten (18%) of the patients reported lower respiratory tract infections including bronchitis, bronchopneumonia, bronchopulmonary aspergillosis, *pneumocystis jirovecii* pneumonia, pneumonia, pseudomonas bronchitis, and pulmonary sepsis, and four (7%) with upper respiratory tract infections, also nasopharyngitis and rhinitis were frequent with 19 (34%) of the patients. 16 (55%) of the patients in the placebo group experienced an infection; most of these (nine [31%]) were nasopharyngitis or rhinitis, but one febrile infection grade 3 and one upper respiratory tract infection grade 4 were reported. General disorders were seen in 28 (50%) of the patients in the lenalidomide group (14 [25%] with fatigue), and nine (31%) of the patients in the placebo group (six [21%] with fatigue). Haematological toxicity was reported in 28 (50%; 20 [36%] with neutropenia) of the patients in the lenalidomide group and in five (16%) patients in the placebo group. Cough (ten [18%]) was frequently reported for patients in the lenalidomide group compared with three (10%) of the patients in the placebo group. Thromboembolic events were infrequent and only occurred in the lenalidomide group: two patients (4%) had deep vein thrombosis, one of grade 3, and one patient (2%) had a grade 4 pulmonary embolism. Polyneuropathy as a known side-effect was observed with CTC grade 1–2 in four (7%) of the patients in the lenalidomide group; however, polyneuropathy was similarly frequent with two patients (7%) in the placebo group.

Neoplasms, benign, malignant or unspecified, were reported in seven (13%) of the patients in the lenalidomide and four (13%) of the patients in the placebo group. Besides one patient with a clonally not related fatal acute lymphocytic leukaemia, there were two patients (4%) with basal cell carcinoma, two (4%) patients with squamous cell carcinoma, and one patient (2%) with prostate cancer observed in the lenalidomide group, and one patient (3%) with basal cell carcinoma and one patient (3%) with squamous cell carcinoma in the placebo group.

Severe events (grade 4 or 5) leading to treatment discontinuation were reported for one patient (2%) with fatal acute lymphocytic leukaemia in the lenalidomide group and one patient (3%) with fatal multifocal leukoencephalopathy in the placebo group, one patient (2%) with grade 4 pulmonary embolism, one (2%) with grade 4 pneumonia and one (2%) with grade 4 neutropenia in the lenalidomide group, one patient (3%) with a grade 4 pulmonary sepsis and one patient (3%) with a grade 4 neutropenia in the placebo group.

Discussion

With the significant prolongation of progression-free survival for physically fit patients with a high risk of progression after first-line treatment, treatment with lenalidomide was more effective than expected according to the study assumptions. Results of studies of maintenance therapies with monoclonal antibodies (rituximab and ofatumumab) and lenalidomide, respectively, prolonging progression-free survival have been published previously.[28–31] The criteria for patients to be eligible for maintenance in previous studies include both patients with complete and partial remissions regardless of their minimal residual disease status or cytogenetic risk factors. We used a different approach with a minimal residual disease-based risk model, including known adverse risk factors such as unmutated *IGHV*-status and *TP53* alterations, to avoid overtreatment in patients expected to have a long progression-free survival after first-line treatment. This strategy allows focusing on a small patient population who might benefit from maintenance treatment using a different mechanism of action than chemoimmunotherapy.

Based on published data,[4] the study design included a progression-free survival assumption for placebo of 22·4 months; however, median progression-free survival for placebo was 13·3 months (95% CI 9·9–19·7). The progression-free survival study assumptions were calculated from day 1 of the first-line treatment. By contrast, the results shown here did not include the time of first-line treatment; progression-free survival was counted from the day of randomisation, which was at least 8 months later than day 1 of the first-line therapy. Taking this difference into account, the results for the placebo cohort confirm the reproducibility of our previously established minimal residual disease (MRD)-based risk prediction. A direct comparison to the progression-free survival of the 379 low-risk patients who were screened but not eligible was not possible, because no further follow-up data were collected for these patients.

The treatment effect for lenalidomide could be shown in both the stratification cohorts and lenalidomide improved the outcome regardless of the MRD level at baseline, similar progression-free survival was prolonged in patients with and without *TP53* aberrations.[32] However, lenalidomide did not overcome the adverse prognostic significance of intermediate versus high level minimal residual disease groups or of *TP53* aberrations. The different outcomes indicate that the progression-free

 Published online September 12, 2017 http://dx.doi.org/10.1016/S2352-3026(17)30171-0

survival is not explained by the study treatment only; minimal residual disease level at baseline still has an effect on the progression-free survival even in patients who received maintenance treatment. Regarding patients with a conversion to minimal residual disease negativity, we wish to emphasise that this is an ongoing study, the number of patients escalated to a higher dose of treatment is expected to increase over time, and the rates of minimal residual disease negative patients should be analysed with more mature data. However, it is interesting to note that in other lenalidomide maintenance studies in chronic lymphocytic leukaemia and other lymphoid malignancies, positive progression-free survival outcome was observed with only modest conversion to MRD negativity or complete remission, raising the possibility that lenalidomide efficacy might be due to factors other than deeper eradication of leukaemia.[33] A detailed multivariate analysis was unfortunately not possible due to the limited event number. Thus, the question regarding the independent prognostic value of both factors remains formally open, but data suggest that both MRD and maintenance treatment effect progression-free survival.

So far, maintenance studies including a study with lenalidomide maintenance failed to show an advantage for overall survival.[33] In our study, overall survival was a secondary endpoint, but because only three events have been reported until data cutoff, a valid statistical comparison between the two study groups was not possible. Of note, the numbers of patients who are still alive in the placebo group were higher than expected. Data collection for this secondary endpoint is still ongoing and might show a trend at least; however, the availability of new treatment options will most probably influence this planned analysis. So far the collected data referring to the subsequent treatments given to relapsed patients were too premature to draw any conclusions. However, the majority of the reported treatments consisted of kinase-inhibitors or BCL2-inhibitors, thus reflecting the better treatment options for patients who did not respond well to first-line treatment.

Using monoclonal antibodies, maintenance treatment was associated with an increased frequency of infections compared with observation alone. Of note, in this study the rate of infections in the lenalidomide group (30 [54%] patients) was not increased compared with the placebo group (19 [66%] patients). The rates of upper respiratory tract infections and common colds were equal; however, grade 3–4 lower respiratory tract infections were more frequent in the lenalidomide group with four (7%) versus one (3%).

This study has several limitations. First, median observation time was rather short with 17·9 months (IQR 9·1–28·1). However, the results of this pre-planned event-triggered interim analysis were robust and reliable from a statistical point of view. Second, the recruitment was incompletely terminated, mainly because there was less interest in this study due to alternative new treatment options for high-risk patients with chronic lymphocytic leukaemia. Though, due to the group-sequential design of the study and the pre-planned analysis there was no lack of power to confirm the primary study hypothesis. Third, first-line regimens were heterogeneous (table 1), with most patients treated with rituximab combined with fludarabine and cyclophosphamide or with bendamustine. Nevertheless, the results for both regimen groups as shown in the supplementary appendix (pp 11–12) indicate that both have benefit from the study treatment with regard to the primary endpoint. The clinical impact of this study might be limited due to the rapid change in chronic lymphocytic leukaemia treatment options over the past 5 years. Although chemoimmunotherapy is still considered a standard first-line option in physically fit patients with low-risk chronic lymphocytic leukaemia without 17p-/*TP53*mut, phase 3 studies examining the combination of new substances compared with chemoimmunotherapy showing a high proportion of MRD-negative responses are already ongoing.[34] Research increasingly focuses on refractoriness to new treatment options. Given the convincing results of this study, the role of lenalidomide in chronic lymphocytic leukaemia might be further investigated, in particular in high-risk patients with chronic lymphocytic leukaemia after first-line therapy with novel agents.[19,20] Lenalidomide or the newer immunomodulatory treatments might play an important part in therapy concepts after the failure of the innovative combinations or for maintaining response to novel combinations in very high-risk chronic lymphocytic leukaemia. Independently of the role of lenalidomide in chronic lymphocytic leukaemia, the findings of this study confirm the prognostic significance of the minimal residual disease-based risk assessment model, which might be used in future trials.

Contributors

AMF, JB, SR, KF, C-MW, HD, MK, SS, SB, BE, and MH designed the study. AMF, JB, SR, OA-S, AA, HH, KJ-U, SD, C-MW, TN, PG, FB, APK, HD, MK, K-AK, ET, SS, MR, SB, BE, and MH were responsible for acquisition, analysis, interpretation of the data. AMF, JB, BE, and MH drafted the report. SR, OA-S, AA, HH, KJU, SD, KF, C-MW, TN, PG, FB, APK, HD, MK, K-AK, ET, SS, MR, and SB revised the report critically for important intellectual content and all authors approved the final version of the manuscript and agreed to be accountable for all aspects related to the accuracy and integrity of the work.

Declaration of interests

AMF received research grants and travel grants from Celgene and grants and personal fees from Hoffmann-la Roche, Mundipharma, and AbbVie. OA-S received personal fees from Gilead, Roche, and AbbVIe. KF received grants from Hoffmann-La Roche. PG received grants and personal fees from AbbVie, Janssen, and Gilead; personal fees from Roche; and grants from Novartis and Celgene. FB received personal fees from Celgene. APK received grants from Celgene. MK received honoraria for participating in advisory boards and research funding from Celgene and Roche. ET received non-financial support from Celgene, GSK, and Amgen; personal fees and non-financial support from Gilead; and grants from Novartis. SS received grants and personal fees from Celgene. MR received grants from the University of Cologne; grants and research support from Hoffmann-La Roche, Celgene, and AbbVie; and consultancy from BMS and Gilead. SB received grants from Celgene and grants and personal fees from AbbVie and Roche.

BE received grants and personal fees from Celgene, Roche, Janssen, AbbVie, and Gilead. MH received research funding from Celgene. JB, SR, AA, HH, KJ-U, SD, C-MW, TN, HD, and K-AK declare no competing interests.

Acknowledgments

We wish to thank all patients and physicians for their participation in the study. Aline Zey and Anne Westermann worked as project managers, Florian Drey and Annette Beer as data managers, and Sabine Frohs as safety manager for the study. We also thank Jean-Pierre Bizzari, Kenichi Takeshita, and Yann Guillevic for their excellent support and cooperation during the conduct of this trial. The study was done with the support of the Competence Net Malignant Lymphoma, Germany, The HOVON trial Center, Amsterdam, Netherlands, PIVOTAL, Madrid, and GELLC, Barcelona, Spain, and CLIOSS in Milan, Italy.

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