CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

LB, VDB, MPM, CM, ET and BF designed the experiments; VDB and CM helped procure the specimens; LB, VDB, AV, GS, SA and ET collected and assembled the data; all authors discussed and interpreted the data, and helped in writing and approval of the manuscript.

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Randomized phase 3 study of lenalidomide versus chlorambucil as first-line therapy for older patients with chronic lymphocytic leukemia (the ORIGIN trial)

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Lenalidomide ((LEN) Revlimid; Celgene Corporation, Summit, NJ, USA), an oral immunomodulatory agent, demonstrated activity in phase 2 trials in patients with chronic lymphocytic leukemia (CLL) in front-line therapy[1,2] and in patients with relapsed and/or refractory disease.[3,4] An open-label, randomized, multicenter, phase 3, parallel-group study was conducted evaluating LEN as first-line therapy for elderly patients ($\geqslant$65 years) with CLL (the ORIGIN trial (NCT00910910)). Chlorambucil (CHB), a standard front-line therapy for elderly patients at trial initiation, was used as a comparator.[5–7]

The study protocol is summarized in the Supplementary Methods. Briefly, between November 2009 and March 2013, 450 CLL patients aged $\geqslant$65 years with previously untreated, active disease and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of $\leqslant$2 were randomized (1:1) to LEN until unacceptable toxicity or progressive disease (PD), or CHB for up to 13 cycles or until unacceptable toxicity or PD. In the LEN arm, patients with creatinine clearance (CrCl) $\geqslant$60 ml/min were given oral LEN 5 mg daily, escalated to 15 mg daily, if tolerated; those with CrCl $\geqslant$30 to $<$60 ml/min were given LEN 2.5 mg daily, escalated to 7.5 mg daily, if tolerated. In the CHB arm, patients received CHB 0.8 mg/kg on days 1 and 15 of each 28-day cycle. The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety, response, duration of response, time to response and overall survival (OS). The study was conducted according to good clinical practice and the ethical principles outlined in the Declaration of Helsinki. All patients provided written informed consent.

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Table 1. PFS and OS by the data cutoff dates (ITT population)

Endpoint	*LEN*			*CHB*			*P-value*
	Median follow-up, months	N	*Median, months (95% CI)*	N	*Median, months (95% CI)*	*HR (90% CI)*	
PFS							
18 February 2013	11.8	212	30.8 (18.7, NE)	215	23.0 (19.3, 29.2)	1.21 (0.88, 1.66)	0.323
26 April 2013	12.6	225	30.8 (18.7, NE)	225	21.4 (19.3, 27.0)	1.00 (0.75, 1.34)	0.994
31 March 2014	18.8	225	30.8 (18.7, NE)	225	21.4 (19.3, 25.1)	0.99 (0.76, 1.29)	0.967
OS							
18 February 2013	11.8	212	NE (NE, NE)	215	NE (NE, NE)	1.69 (1.06, 2.67)	0.060
26 April 2013	12.6	225	NE (NE, NE)	225	NE (35.8, NE)	1.46 (0.95, 2.26)	0.149
31 March 2014	18.8	225	NE (NE, NE)	225	44.0 (37.3, NE)	1.03 (0.73, 1.46)	0.883

Abbreviations: CHB, chlorambucil; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; LEN lenalidomide; NE, not estimable; OS, overall survival; PFS, progression-free survival.

The data monitoring committee observed an imbalance in deaths between the treatment arms favoring CHB in February 2013. As a result, patients aged $\geqslant$81 years discontinued study treatment in April 2013, and all patients receiving LEN discontinued treatment in July 2013. By March 2014, all patients in the CHB arm had also stopped treatment. Patient flow and the rationale for the data cutoff dates are provided in Supplementary Figure 1 and Supplementary Table 1, respectively.

Median age was 72 years (range 65–90) and 73 years (range 65–92) in the LEN and CHB arms, respectively. Baseline characteristics were well balanced between treatment arms (Supplementary Table 2). More patients in the LEN arm had an ECOG PS score of 0 compared with the CHB arm.

Median PFS at the February 2013 cutoff date (median follow-up 11.8 months) was 30.8 months in the LEN arm versus 23.0 months in the CHB arm. The hazard ratio (HR) for PD or death favored the CHB arm but was not statistically significant (HR 1.21; 90% confidence interval (CI) 0.88–1.66; $P=0.323$). There were 35 deaths (16.5%) in the LEN arm and 21 (9.8%) in the CHB arm. The HR for OS was 1.69 (90% CI 1.06–2.67; $P=0.060$) in favor of CHB. Similar results were seen at the April 2013 cutoff date, when all patients aged $\geqslant$81 years discontinued treatment (Table 1). As of March 2014, 94 of the 450 patients had died (20.9%), with an equal number in each treatment arm (47/225; 20.9%). The HR for OS was 1.03 (90% CI 0.73–1.46; $P=0.883$; Supplementary Figure 2).

Overall response rate at the April 2013 cutoff date was significantly lower in the LEN arm than the CHB arm (55.1 vs 65.8%; $P=0.026$). Complete response (CR) was achieved in 6 (2.7%) LEN-treated patients and 22 (9.8%) CHB-treated patients. Median time to first response was 8.9 weeks for LEN-treated patients versus 8.1 weeks for CHB-treated patients. Median duration of response had not been reached for LEN-treated patients versus 87.1 weeks for CHB-treated patients. The HR for duration of response favoring LEN was 0.74 (90% CI 0.47–1.16; $P=0.262$).

Median treatment duration at the April 2013 cutoff was shorter in the LEN arm compared with the CHB arm (207 vs 293 days, respectively), with greater frequency of treatment discontinuations due to treatment-emergent adverse events (TEAEs) in the LEN arm. Median number of treatment cycles was 7 in the LEN arm and 10 in the CHB arm. Median dose intensity was 4.9 mg per day in the LEN arm. More patients in the LEN arm than in the CHB arm had study drug interrupted and/or reduced due to adverse events (AEs; 63.8 vs 21.1%, respectively). Neutropenia was the most frequently reported TEAE, leading to dose reduction/interruption in either treatment arm. More patients in the LEN arm had dose reductions/interruptions due to neutropenia than patients in the CHB arm (31.3 vs 11.2%, respectively).

TEAEs were reported by more LEN-treated patients than CHB-treated patients (95.1 vs 90.1%, respectively; Supplementary Table 3) as were grade 3, 4 and 5 TEAEs (37.9 vs 32.3%; 34.4 vs 20.6%; and 9.4 vs 4.9%, respectively; Supplementary Table 4). Serious TEAEs were reported more frequently in the LEN versus CHB arm (63.8 vs 38.6%, respectively), including neutropenia (23.7 vs 14.3%), pneumonia (10.7 vs 2.7%), thrombocytopenia (8.0 vs 5.8%) and anemia (7.6 vs 4.0%). Tumor flare (serious and/or grade $\geqslant$3) in the LEN arm tended to occur early in treatment (13 of 18 events in the first year occurred $\leqslant$1 month of treatment), with none in the CHB arm.

TEAEs leading to treatment discontinuation were higher with LEN than CHB (29.0 vs 17.5%, respectively). The most frequently reported ($\geqslant$2%) TEAEs leading to discontinuation were thrombocytopenia, pneumonia and tumor flare for LEN and neutropenia, anemia and thrombocytopenia for CHB.

At the April 2013 cutoff date, 61 deaths had occurred—36 (16.0%) in the LEN arm and 25 (11.1%) in the CHB arm. The primary causes of death are shown in Table 2. No single cause of death appeared responsible for the higher number of deaths in the LEN arm. Most deaths occurred $\leqslant$9 months after treatment initiation. More deaths occurred in the LEN arm within 6 months of starting treatment (6.2 vs 5.3%, respectively), and from 6–9 months following the start of treatment (4.0 vs 0.9%, respectively) compared with CHB. Thereafter, the frequency of deaths was similar for the two treatment arms. The median age of LEN-treated and CHB-treated patients who died was 74.5 years and 75.0 years, respectively.

More deaths were observed among older LEN-treated patients: in the overall LEN-treated population, 11.6% of patients were aged $>$80 years; however, 27.8% of those patients who died were $>$80 years. Of the 26 LEN-treated patients aged $>$80 years, 10 patients (38.5%) died compared with 26 (13.1%) of 199 LEN-treated patients aged $\leqslant$80 years. Over-representation of deaths in older patients was not observed in the CHB arm where the proportions of patients $>$80 years (11.1%) and patients $>$80 years who died (12.0%) were similar. Fewer deaths occurred in responders than in non-responders: 10.5 vs 22.8%, respectively, in the LEN arm, and 6.1 vs 20.8%, respectively, in the CHB arm.

LEN-treated patients who died were more likely to have had baseline comorbidities requiring treatment and/or a more complex medical history than CHB-treated patients (Supplementary Table 5). A higher proportion of LEN-treated versus CHB-treated patients who died had a positive baseline Coombs test (22.2 vs 12.0%), bulky disease (lymphadenopathy $>$5 cm; 30.6 vs 16.0%), baseline ECOG PS of 2 (19.4 vs 4.0%) and IgG levels $<$700 mg/dl (47.2 vs 28.0%). These characteristics were also present in a higher proportion of LEN-treated patients who died, versus the overall LEN-treated population.

Table 2. Investigator-assessed primary cause of death by MedDRA SOC: 26 April 2013 (ITT population)

SOC	n *(%) patients*	
	LEN (N = *225*)	*CHB* (N = *225*)
Deaths	36 (16.0)	25 (11.1)
General disorders and administration site conditions		
Death	4 (1.8)	3 (1.3)
Disease progression	3 (1.3)	2 (0.9)
Multi-organ failure	3 (1.3)	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Chronic lymphocytic leukemia	4 (1.8)	5 (2.2)
Refractory chronic lymphocytic leukemia	0 (0.0)	1 (0.4)
Hodgkin lymphoma	1 (0.4)	0 (0.0)
Metastatic small intestine carcinoma	1 (0.4)	0 (0.0)
Cardiac disorders		
Cardiac arrest	3 (1.3)	0 (0.0)
Cardiopulmonary failure	2 (0.9)	0 (0.0)
Cardiac failure	1 (0.4)	3 (1.3)
Pericardial effusion	1 (0.4)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.4)
Infections and infestations		
Pneumonia	5 (2.2)	3 (1.3)
Respiratory tract infection	1 (0.4)	0 (0.0)
Sepsis	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders		
Respiratory failure	1 (0.4)	0 (0.0)
Acute respiratory failure	0 (0.0)	1 (0.4)
Respiratory distress	0 (0.0)	1 (0.4)
Blood and lymphatic system disorders		
Autoimmune hemolytic anemia	1 (0.4)	1 (0.4)
Gastrointestinal disorders		
Lower gastrointestinal hemorrhage	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders		
Tumor lysis syndrome	1 (0.4)	0 (0.0)
Nervous system disorders		
Intracranial hemorrhage	1 (0.4)	0 (0.0)
Psychiatric disorders		
Suicide	1 (0.4)	0 (0.0)
Renal and urinary disorders		
Renal failure	1 (0.4)	0 (0.0)
Injury, poisoning and procedural complications		
Post-procedural hemorrhage	0 (0.0)	1 (0.4)
Skull fracture	0 (0.0)	1 (0.4)

Abbreviations: CHB, chlorambucil; ITT, intention-to-treat; LEN, lenalidomide; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.

A greater proportion of patients who died had moderate renal impairment (CrCl $\geqslant$ 30 to $<$ 60 ml/min). In the LEN arm, 39.1% of patients overall had moderate renal impairment, whereas of patients who died, 58.3% had moderate renal impairment. In the CHB arm, the incidence of moderate renal impairment was 43.6% overall, and 56.0% in the patients that died.

As of March 2014, a total of 20 (8.9%) patients in the LEN arm versus 32 (14.3%) in the CHB arm experienced $\geqslant$ 1 second primary malignancy (SPM). A lower proportion of patients in the LEN arm experienced an invasive SPM (hematologic and solid tumor) versus the CHB arm (3.6 vs 6.3%, respectively). Hematologic SPMs occurred in 3 (1.3%) vs 4 (1.8%) patients in the LEN versus CHB arm, respectively; solid tumor SPMs occurred in 5 (2.2%) versus 10 (4.5%) patients, respectively.

At the March 2014 cutoff date, approximately one-third of patients in the LEN (36.6%) and CHB arms (33.6%) had received subsequent anticancer therapies. As there was no apparent imbalance between the treatment arms, the use of subsequent anticancer therapies was not believed to have confounded the OS results.

On the basis of these interim results of a trial that was terminated early, it appears that LEN did not prolong PFS and was associated with a lower response rate, a higher incidence of grade $\geqslant$ 3 AEs and a higher number of deaths compared with CHB. Although LEN demonstrated clinical activity in a subset of patients in this trial, LEN monotherapy is not recommended as first-line therapy for patients with CLL, particularly those who are elderly and/or frail. Further research will be required to determine whether future immunomodulatory agents could have a role in the treatment of CLL.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

AC-K and JGG participated in protocol development and review. All authors participated in collecting and/or analyzing the data reported in this study. All authors provided direction into the development of the manuscript and were fully responsible for content and editorial decisions.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)

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Genomic landscape characterization of large granular lymphocyte leukemia with a systems genetics approach

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Large granular lymphocyte (LGL) leukemia is a rare clonal disease characterized by a persistent increase in the number of CD8+ cytotoxic T cells or CD16/56+ natural killer (NK) cells. It is associated with recurrent infections, severe cytopenias and autoimmune diseases. JAK/STAT pathway activation, deregulation of pro-apoptotic pathways (sphingolipid and FAS/FAS ligand) and activation of pro-survival signaling pathways (PI3K/AKT and RAS) are known hallmarks of LGL leukemia. Activating somatic *STAT3* mutations have been reported in the SH2 domain (30–70% of cases),[1–3] and in the DNA-binding or coiled-coil domain (2%).[4] *STAT5B* mutations are more rare, but typical of CD4+ T-LGL leukemia cases.[5–7] The JAK/STAT pathway can also be activated by non-mutational mechanisms such as increased interleukin-6 (IL-6) secretion and epigenetic inactivation of JAK-STAT pathway inhibitors.[8] Indeed, aberrant *STAT* signaling is observed in almost all LGL leukemia patients irrespective of the presence of JAK/STAT mutations.[9]

To characterize the genomic landscape of LGL leukemia, we performed whole-exome sequencing (Supplementary Methods and Supplementary Figure 1) from 19 paired tumor-control samples derived from untreated LGL leukemia patients including conventional CD8+ ($n = 13$) T-cell cases, and more rare CD4+ or CD4+CD8+ T-cell cases ($n = 3$), and NK LGL leukemias ($n = 3$; Supplementary Table 1). Eleven STAT-mutation-negative patients were included for identification of new driver mutations. All sequenced samples were highly purified sorted cell populations (either CD8+ or CD4+ T cells or NK cells), and T-cell receptor Vbeta analysis confirmed monoclonal expansions in the tumor fractions of T-cell cases (see Supplementary Methods and Supplementary Table 1). The average sequencing coverage in the tumor samples was 32x (Supplementary Figure 2). Both the coverage and the number of raw called variants were similar in tumor and control samples. After selecting high confidence variants (see Supplementary Methods), and filtering out variants already described in human populations single nucleotide polymorphism database and/or with allele frequency higher than 5% in exome aggregation consortium exomes, 28 508 somatic variants in 16 518 genes were identified in the whole cohort with a high prevalence of C>T and G>A transversions (Supplementary Figure 3A). Next, among high confidence and rare variants, we selected 370 variants in 347 genes with a strong predicted functional impact (Supplementary Methods and Supplementary Table 2). The observed differences in numbers of somatic mutations (range 5–40, average 20) and genes involved (range 4–41, 19) per patient were not because of coverage differences (Supplementary Figure 3B). A slight tendency toward more mutated genes per patient in STAT-mutation-positive (22.9 in average) versus negative patients (18.4 in average) was noticed. Sanger sequencing validations of somatic variants were obtained in 14 genes (Supplementary Table 3 and Supplementary Figure 4) being recurrent or prioritized according to functional criteria and/or connections emerged by integrated pathway-derived networks. The positions of the mutations in protein domains of selected genes are shown in Supplementary Figure 5.

In addition to *STAT3* (all in CD8+ T-LGL) and *STAT5B* (CD4+ and CD8+ cases) mutations (in 8/19 patients, 42%), 14 other genes had recurrent mutations including transcriptional/epigenetic regulator, tumor suppressor and cell proliferation genes (Figure 1a and 2a). *KMT2D* has been linked to lymphomagenesis[10] and found to be frequently mutated in other cancers. Mutations of *PCLO*, a calcium sensor-regulating cAMP-induced exocytosis, have been previously reported in diffuse large B-cell lymphoma. *FAT4* is an upstream regulator of stem cell genes both during development and cancer, functioning as a tumor growth suppressor via activation of Hippo signaling. It was previously found recurrently mutated in human cancers, including leukemias. Also the other recurrently mutated gene, *ARL13B,* is linked to Hippo signaling. It encodes a small

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