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# Impact of lenalidomide consolidation on health-related quality of life in chronic lymphocytic leukemia: ancillary study of the phase III CLL6-RESIDUUM trial

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## Abstract

**Background** Within the French-Australian CLL6 RESIDUUM trial, an ancillary study aimed at assessing the health-related quality of life (HRQoL) of patients with chronic lymphocytic leukemia (CLL) receiving a two-year consolidation of lenalidomide (LEN) or observation (OBS) after classical immunochemotherapy leaving them with detectable residual disease.

**Methods** Data from French patients involved in this the trial were used here. The EORTC QLQ-C30 version 3 questionnaire was completed by patients at baseline, and then at months 3, 6, 12, 18 and 24 after consolidation. Repeated measures mixed-effects models were used to assess HRQoL changes between baseline and each checkpoint for each HRQoL scale.

**Results** Baseline data showed overall a good global health status with mean scores of 76.3 and 72.1 in the LEN and OBS arms respectively, on the 0–100 scale. At 12 months, LEN patients had significantly more diarrhea than OBS patients ($p=0.003$) and social functioning was significantly impaired at month 18 ($p=0.05$). A 10-point difference appeared in the LEN arm for dyspnea and digestive disorders from month 12 on. Multivariate analysis showed a deleterious effect of LEN on global health ($p=0.02$) and functional scales ($p=0.003$).

**Conclusion** This study provides HRQoL values in a French cohort of CLL patients in consolidation treatment. Supplementation with lenalidomide as consolidation therapy in CLL leads to late health deterioration, especially diarrhea, after 12 months of treatment. Quantitative assessment of HRQoL should be balanced against benefits in disease control to determine overall health benefits.

**Keywords** Chronic lymphocytic leukemia, Health-related quality of life, Patient-reported outcomes, Lenalidomide, Clinical trial

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## Background

Several studies in the early 2000's demonstrated the capacity of the immunomodulating drug (IMiD) lenalidomide, given in association with standard treatment regimens, to improve remission rates and survival of patients with multiple myeloma, non-Hodgkin lymphoma or myelodysplastic syndromes [1–3]. Chronic lymphocytic leukemia (CLL) was also the subject of some trials involving lenalidomide. For instance, two phase II studies at the Roswell Park Cancer Institute and at the MD Anderson Cancer Center showed that lenalidomide helped to achieve major responses in approximately 30—50% of patients with chemorefractory CLL, with little or no infectious toxicity [4, 5]. Progression-free survival was significantly longer in the lenalidomide than in the placebo group in the randomized study by Chanan Khan et al. [4]. The final analysis of CLL6 RESIDUUM study showed a significant benefit of consolidation therapy with lenalidomide in CLL patients with residual disease after FCR treatment [5]. However, fatigue, thrombocytopenia and neutropenia were severe side effects of lenalidomide supplementation. In the work of Ferrajoli et al. [6], clinical improvement was associated with early increases in median interleukin (IL)-6, IL-10, IL-2, and tumor necrosis factor receptor-1 levels, supporting the antitumor efficacy of the immunomodulator drug, while myelosuppression was the major side-effect.

Based on these results, the CLL6 RESIDUUM trial was designed to explore the potential efficacy of lenalidomide as consolidation therapy in patients with CLL in complete (CR) or partial (PR) response, with detectable measurable residual disease (MRD) after a classical immunochemotherapy (ICT) treatment with fludarabine, cyclophosphamide and rituximab (FCR). This joint study of the Australasian Leukaemia and Lymphoma Group (ALLG) and the French CLL branch of the French Innovative Leukemia Organization (FILO) randomized the patients in a 1:1 ratio to receive two years of consolidation treatment with lenalidomide or enter an observation arm. An ancillary study was planned to examine the effects of this supplementation on health-related quality of life (HRQoL) and patient-reported outcomes (PRO) throughout the two-year consolidation or observation period.

## Methods

### Patients and study design

The CLL6 RESIDUUM trial was a phase III randomized clinical trial of the ALLG and the FILO. Eligibility criteria were CLL patients with detectable residual disease after front-line ICT according to iwCLL guidelines [7]. Patients should have received at least 4 and at most 6 cycles of FCR. Residual disease was considered when detected at a level of at least $10^{-4}$ in multiparameter flow cytometry of peripheral blood or bone marrow, or when visualized through radiological evaluation. After enrolment, patients were randomized 1:1 to receive a daily dose of 10 mg lenalidomide (LEN arm) for two years or no treatment (observation, OBS arm). The primary end point of the study was time to progression (progression free survival, PFS) or death. An exploratory objective of this trial was to assess quality of life (QoL) using the EORTC QLQ-C30. Initially, this manuscript reported only the prospective QoL data for the French patients in this part of the trial. In a second part, a further study will be carried out with QoL data from Australian patients and the results will be compared.

The protocol was approved by the French National Competent authority (Agence Nationale de Sécurité du Médicament, Reference: 131618A-11) and an Ethics Committee (CPP de Sud Méditerranée I, Reference: 14 05). The study was performed according to the principles of the Declaration of Helsinki. All patients provided written informed consent to participate. The trial was registered on 19 January 2010 in the Australian New Zealand Clinical Trials Registry under the number: ACTRN12610000060044.

**Table 1** French cohort characteristics

| Variables | Whole population (*N* = 66) | Lenalidomide (*N* = 32) | Observation (*N* = 34) |
|---|---|---|---|
| Age at randomization, years | | | |
| Mean (SD) | 69 (8.3) | 69 (8.86) | 69 (7.86) |
| Median (min–max) | 69.5 [48–83] | 71.5 [48–83] | 68 [53–83] |
| Age range, N (%) | | | |
| < 70 | 33 (50) | 14 (44) | 19 (56) |
| ≥ 70 | 33 (50) | 18 (56) | 15 (44) |
| Sex, N (%) | | | |
| Women | 20 (28) | 9 (26) | 11 (30) |
| Men | 46 (72) | 23 (74) | 23 (70) |
| Positive MRD at baseline | | | |
| Yes | 61 (92) | 29 (91) | 32 (94) |
| No | 5 (8) | 3 (9) | 2 (6) |
| Follow-up, N (%) | | | |
| Expected end of study | 44 (67) | 18 (56) | 26 (76) |
| Out at 12 months | 8 (12) | 6 (19) | 2 (6) |
| Out at 18 months | 11 (17) | 7 (22) | 4 (12) |
| Out at 24 months | 3 (4) | 1 (3) | 2 (6) |

### Patient-reported outcomes

Patient reported outcomes (PROs) were assessed through the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3. This is a 30-item cancer questionnaire with one global health, five functional and nine symptom scales. This is a validated questionnaire used to assed HRQoL of patients with CLL in other longitudinal study [8]. Respondents are asked to rate the severity of their estimated HRQoL burden over the past 7 days. A score (range 0–100) is generated for each scale through a specific tool of the EORTC that calculates the mean QoL scores for each dimension. High scores for the global health scale and for the 5 functioning scales denote a good/better level of HRQoL. Conversely, high scores on the symptom scales indicate a poorer HRQoL.

Patients were asked to complete the questionnaire at baseline and at the end of months 3, 6, 12, 18 and 24 after consolidation. PROs were compared between the two arms, respectively LEN and OBS. The evolution of scores over time was also analyzed in each arm.

### Statistical analyses

Scores from EORTC QLQ-C30 were descriptively summarized according to treatment arm. Repeated measures mixed-effects models were used to assess the mean HRQoL changes from baseline to each checkpoint and for each scale. The models were adjusted on age ($<70$ vs. $\geq 70$) and pattern (patient follow-up trends) as well as any time trends associated with the repeated measurements.

A significance level of $p<0.05$ was considered statistically significant. A difference of $\geq 10$ points between groups was deemed a clinically significant result [9], in

**Table 2** Short-term HRQoL following Lenalidomide versus Observation

| Scales EORTC QLQ-C30 (v3) | Baseline | | | 3 months | | | 6 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lenalidomide (*N* = 32) Mean (SD) | Observation (*N* = 34) Mean (SD) | *P* value | Lenalidomide (*N* = 26) 81%[§] Mean (SD) | Observation (*N* = 29) 85%[§] Mean (SD) | *P* value | Lenalidomide (*N* = 28) 87%[§] Mean (SD) | Observation (*N* = 29) 85%[§] Mean (SD) | *P* value |
| **Global health**[a] | 76.3 (14.7) | 72.1 (17.9) | 0.1 | 75 (13.3) | 78.6 (16.4) | 0.228 | 70.7 (19.9) | 76.7 (17) | 0.100 |
| **Functional subscale**[b] | | | | | | | | | |
| Physical functioning | 90.2 (9.5) | 87.1 (15.5) | 0.3 | 88.6 (11.1) | 88.6 (13.9) | 0.314 | 87.6 (10) | 90.1 (12.3) | 0.073 |
| Role functioning | 87.4 (22.8) | 89 (16.6) | 0.4 | 86.4 (21.7) | 90.5 (16) | 0.302 | 85.2 (19.6) | 91.4 (17) | 0.079 |
| Emotional functioning | 84.2 (20.4) | 77.7 (22.6) | 0.08 | 86.3 (17) | 84.5 (20.2) | 0.472 | 85.5 (17.4) | 83.9 (18.9) | 0.452 |
| Cognitive functioning | 90.4 (13.2) | 87.6 (16.3) | 0.2 | 87.6 (13.5) | 84.5 (19.7) | 0.424 | 88.3 (13.7) | 87.3 (14.5) | 0.422 |
| Social functioning | 92.4 (13.9) | 89 (16.1) | 0.1 | 92.6 (17.5) | 85.7 (27.8) | 0.138 | 87.6 (19.9) | 91.9 (20.2) | 0.092 |
| **Symptom subscale**[c] | | | | | | | | | |
| Fatigue | 19.7 (20.5) | 30.5 (25.5) | **0.03**[*] | 21.8 (21.2) | 26.6 (23.9) | 0.225 | 27.2 (16.1) | 23 (21.2) | 0.145 |
| Nausea and vomiting | 2 (9.1) | 5.7 (12.7) | **0.03** | 4.3 (8.8) | 6.54 (19.4) | 0.481 | 2.4 (6) | 4 (8.5) | 0.273 |
| Pain | 17.7 (26.3) | 20.9 (25.7) | 0.238 | 11.1 (19) | 16.1 (27) | 0.422 | 16 (20.4) | 12.1 (18.8) | 0.211 |
| Dyspnea | 15.6 (25.4) | 17.1 (23.4) | 0.31 | 18.5 (23.3) | 10.7 (18.3) | 0.096 | 19.7 (21.2) | 12.6 (18.7) | 0.092 |
| Insomnia | 15.1 (23.7) | 34.3 (33.8) | **0.006**[*] | 27.2 (30.7) | 27.4 (27.3) | 0.417 | 23.1 (30.9) | 19.5 (26) | 0.400 |
| Appetite loss | 10.1 (22.8) | 12.4 (29.2) | 0.415 | 4.9 (15.2) | 10.7 (20.4) | 0.098 | 2.5 (12.8) | 10.3 (23.7) | **0.033** |
| Constipation | 6.1 (15.5) | 17.1 (28.4) | **0.04**[*] | 17.3 (31.2) | 19.7 (31) | 0.320 | 19.7 (26.6) | 17.2 (29) | 0.260 |
| Diarrhea | 13.1 (23.5) | 11.4 (22.8) | 0.348 | 6.7 (13.6) | 8.4 (21.5) | 0.453 | 9.9 (18) | 5.7 (12.8) | 0.204 |
| Financial difficulties | 10.1 (25.7) | 9.5 (22.2) | 0.359 | 11.1 (29.2) | 11.9 (22.6) | 0.163 | 11.1 (27.7) | 8 (21.2) | 0.432 |

*P* value calculated from comparison between lenalidomide and observation group

[a] A high score for the Global health status represents a high Quality of life

[b] A high score for a functional subscale represents a high / healthy level of functioning

[c] A high score for a symptom subscale represents a high level of symptomatology or problems

[*] Values with more than 10 points difference between the means

[§] Proportion of respondents completing the QoL questionnaire at each time point by baseline

**Table 3** Long-term HRQoL following lenalidomide versus observation

| Scales EORTCQLQ-C30 (v3) | 12 months | | | 18 months | | | 24 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lenalidomide (*N* = 23) 72%[§] Mean (SD) | Observation (*N* = 33) 97%[§] Mean (SD) | *P* value | Lenalidomide (*N* = 17) 53%[§] Mean (SD) | Observation (*N* = 27) 79%[§] Mean (SD) | *P* value | Lenalidomide (*N* = 18) 56%[§] Mean (SD) | Observation (*N* = 27) 79%[§] Mean (SD) | *P* value |
| **Global health**[a] | 74.3 (18.9) | 75.7 (17.7) | 0.412 | 75.5 (17.6) | 73.4 (17.8) | 0.434 | 75 (11.1) | 76.2 (17.8) | 0.204 |
| **Functional subscale**[b] | | | | | | | | | |
| Physical functioning | 85.8 (13.5) | 89.1 (14.3) | 0.100 | 89 (11.5) | 91.8 (10.4) | 0.210 | 88.2 (10.4) | 93.3 (7.8) | 0.054 |
| Role functioning | 86.9 (18.8) | 88.4 (19.3) | 0.340 | 80.4 (27.1) | 91 (15.1) | 0.340* | 85.3 (22.7) | 94.9 (13.1) | 0.057 |
| Emotional functioning | 81.1 (25.8) | 85.6 (14.9) | 0.493 | 79.4 (18.4) | 84.9 (16.8) | 0.157 | 79.2 (22.2) | 85.3 (21.4) | 0.148 |
| Cognitive functioning | 84 (19.1) | 90.9 (13.2) | 0.084 | 87.2 (19.1) | 83.3 (17) | 0.135 | 89.8 (12.9) | 90.7 (13.3) | 0.382 |
| Social functioning | 83.3 (29.3) | 92.4 (18.2) | 0.053 | 86.3 (25.9) | 96.8 (8.2) | **0.050*** | 83.3 (29.1) | 93.8 (12.3) | 0.145* |
| **Symptom subscale**[c] | | | | | | | | | |
| Fatigue | 26.1 (21.3) | 18.3 (16.6) | 0.086 | 26.8 (21.9) | 20.1 (16.9) | 0.164 | 21.6 (15.4) | 18.2 (15.4) | 0.201 |
| Nausea and vomiting | 3.6 (8.6) | 5.1 (10.6) | 0.346 | 0 (0) | 2.6 (7.7) | 0.080 | 0 (0) | 3.8 (8.6) | **0.030** |
| Pain | 20.3 (22) | 16.7 (20.8) | 0.222 | 27.4 (27.6) | 12.8 (19) | **0.025*** | 13.9 (20) | 14.8 (21.3) | 0.463 |
| Dyspnea | 23.2 (29.2) | 13.1 (16.5) | 0.137* | 19.6 (20.6) | 7.7 (14.3) | **0.020*** | 23.5 (25.7) | 9 (17.8) | **0.019*** |
| Insomnia | 30.4 (31.6) | 25.2 (23.6) | 0.334 | 27.45 (31.7) | 21.8 (26.6) | 0.313 | 21.5 (31) | 17.9 (19.4) | 0.472 |
| Appetite loss | 4.3 (11.5) | 9.1 (19.1) | 0.201 | 11.8 (23.4) | 5.1 (15.4) | 0.149 | 5.9 (17.6) | 7.7 (19.6) | 0.378 |
| Constipation | 15.9 (19.8) | 11.1 (18) | 0.162 | 9.8 (19.6) | 20.5 (32.7) | 0.175* | 16.7 (26.2) | 7.4 (14.1) | 0.144* |
| Diarrhea | 20.3 (21.9) | 7.1 (18.2) | **0.003*** | 39.2 (37.7) | 6.4 (16.4) | **0.0003*** | 48.1 (30.7) | 13.6 (21.2) | **0.0001*** |
| Financial difficulties | 13 (29.7) | 7.1 (20) | 0.250 | 15.7 (29.1) | 6.9 (13.8) | 0.218 | 14.8 (30.7) | 2.5 (8.9) | 0.065* |

*P* value calculated from comparison between lenalidomide and observation group

[a] A high score for the Global health status represents a high Quality of life

[b] A high score for a functional subscale represents a high / healthy level of functioning

[c] A high score for a symptom subscale represents a high level of symptomatology or problems

[*] Values with more than 10 points difference between the means

[§] Proportion of respondents completing the QoL questionnaire at each time point by baseline

line with common practice for interpreting EORTC-QLQ-C30 scores for longitudinal changes [10].

All analyses were performed using SAS software, version 9.4.

## Results

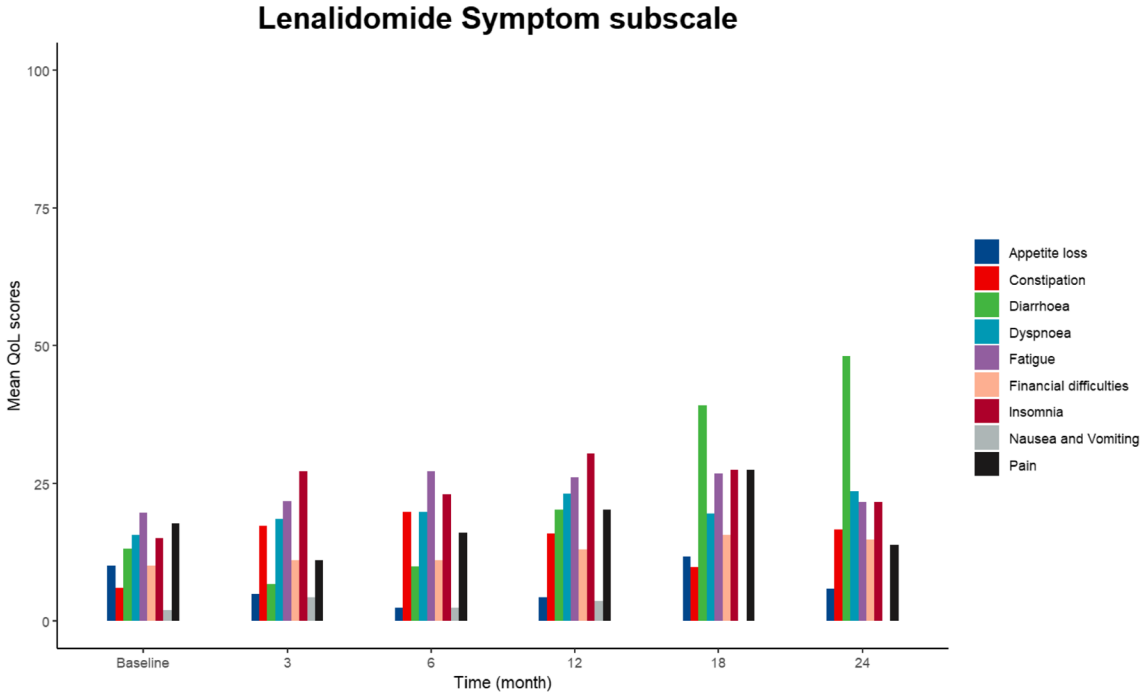
### Patient characteristics

Of 73 patients enrolled in France between July 2014 and March 2017, HRQoL data were available for 66 at baseline, respectively 32 in the LEN and 34 in the OBS arms. Their characteristics are summarized in Table 1. Half of the patients in each arm were over 70-year-old. There was a predominance of men in both groups. At the end of the study, 45 questionnaires were still available for evaluation. Of note, analysis of the whole (French and Australian patients) cohort demonstrated a significantly longer progression-free survival in the LEN group [11].

### EORTC QLQ-C30 results (Tables 2 and 3)

Baseline data showed overall a good global health status with mean scores of 76.3 and 72.1 in the LEN and OBS groups respectively, on the 0–100 scale. Similarly, good functional scores ranged between 77.7 and 92.4. All these scores, except role functioning, were slightly higher in the LEN group. There was no statistically significant difference between the two arms for these two scales. Scores in the symptom subscale were accordingly in the low values, the highest being 34.3 for insomnia in the OBS group. Of note, this value was significantly lower in the LEN group ($p = 0.006$). Patients in the OBS arm also reported significantly more fatigue ($p = 0.03$), nausea/vomiting ($p = 0.03$) and constipation ($p = 0.04$). All other items were similar, slightly higher in the OBS group except for financial difficulties.

**a Lenalidomide arm**




**b Observation arm**

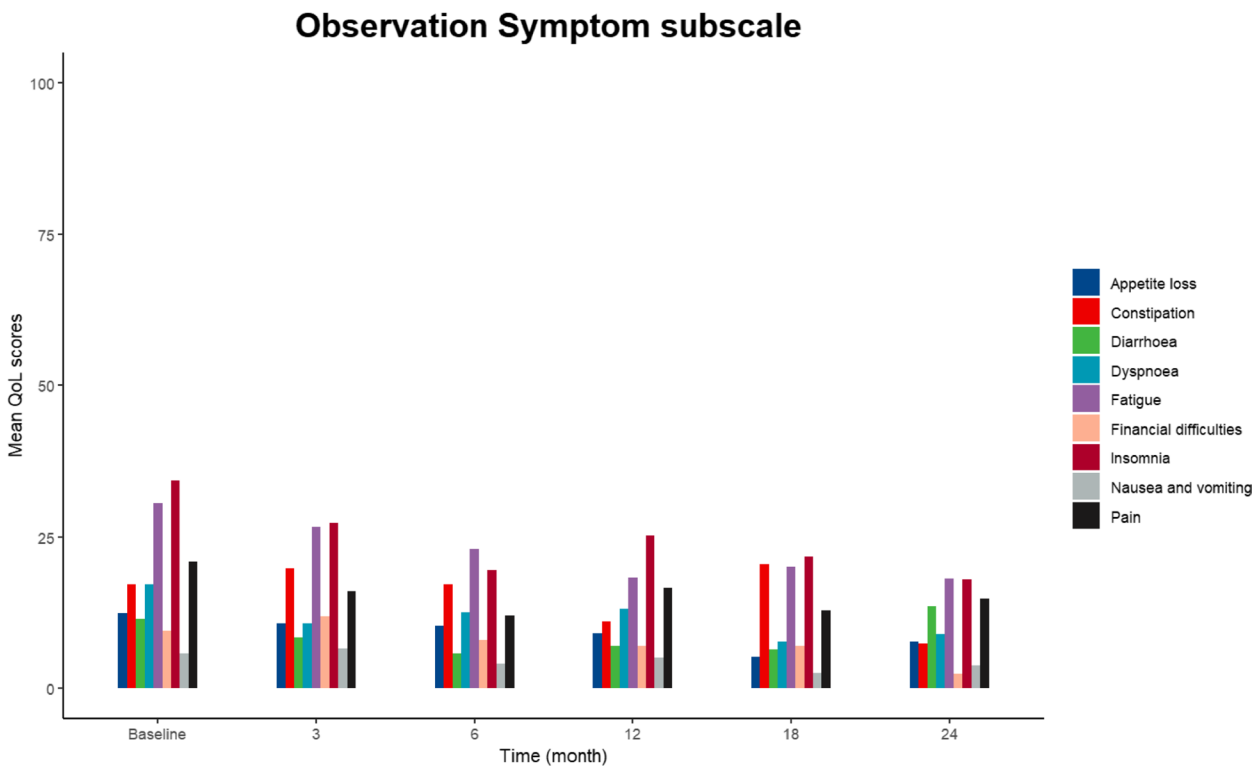



**Fig. 1** Graphical representation of changes in HRQoL symptoms over time. Higher values indicate more symptoms

Good global health and functioning scores and low symptoms persisted after 3 months, without any significant difference between the two treatment arms. At six months, there was however more appetite loss in the OBS arm ($p=0.033$), this being the only significant difference.

The potentially deleterious effect of lenalidomide became progressively visible, with significant differences from month 12 on. At that stage, LEN patients had significantly more diarrhea than OBS patients ($p=0.003$). Social functioning was significantly impaired at month 18 ($p=0.05$), confirming a trend that had appeared at month 6 and persisted at 2 years. Most symptoms also steadily increased in the LEN group, with statistically significant differences for dyspnea and diarrhea at months 18 and 24 ($p$ values of 0.02, 0.019, 0.0003 and 0.0001 respectively). There was also more pain reported at month 18 ($p=0.025$) and nausea/vomiting at month 24 ($p=0.03$).

Taking into account the clinical significance of a 10-point difference mentioned above (asterisks in Tables 2 and 3), this was present at baseline for fatigue, insomnia and constipation, worse in patients from the OBS arm. Under consolidation therapy, differences appeared in the LEN arm for dyspnea and digestive disorders from month 12 on. Moreover, role and social functioning differed at 18 months for this arm, together with pain. Social functioning remained clinically different at month 24. The difference was always due to higher values (i.e. poorer QoL) in the LEN arm during consolidation therapy.

As shown in Fig. 1, most symptoms showed a trend for increase over time in the LEN arm and a decrease in the OBS arm. This is computed in Table 4 comparing, for each arm, baseline and month 24 assessments. Global health PROs remained stable in the LEN arm and increased slightly in the OBS arm. More functional subscales decreased in the LEN arm, respectively physical, emotional and social functioning (Fig. 2). Of note, standard deviations are rather high in this table, especially for emotional functioning, indicating that this impact could have been important in some patients. Conversely, there was an improvement of global health and all functioning features in the OBS arm.

Severe alterations of dyspnea, insomnia, constipation and mainly diarrhea were noticed in the LEN arm (Fig. 1a). In opposition, and in line with the progressive decrease shown in Fig. 1b, seven of the nine symptoms assessed improved in the OBS arm, with only a small trend of alteration for nausea/vomiting and diarrhea.

**Table 4** Mean change from baseline to month 24 in QoL measures according to treatment

| | Mean change from baseline to month 24 | |
|---|---|---|
| | **Lenalidomide Mean (SD)** | **Observation Mean (SD)** |
| EORTC QLQ-C30 parameter | | |
| Global health | 0 (12.5) | 1.7 (12) |
| **Functional subscale** | | |
| Physical functioning | -1.4 (8.7) | 3.3 (8.8) |
| Role functioning | 1.1 (9.9) | 4.2 (11.3) |
| Emotional functioning | -1.2 (16) | 4 (19.9) |
| Cognitive functioning | 2.1 (13.4) | 2.7 (15.7) |
| Social functioning | -1.1 (9.6) | 0.7 (17) |
| **Symptom subscale** | | |
| Fatigue | 1.1 (16.5) | -9.5 (19.9) |
| Nausea and vomiting | -1.1 (4.3) | 2.1 (10.2) |
| Pain | -3.1 (20.4) | -4.7 (20.1) |
| Dyspnea | 9.5 (20.4) | -2.8 (19.5) |
| Insomnia | 4.4 (21.3) | -12.5 (33.8) |
| Appetite loss | -2.2 (8.6) | -4.1 (31.6) |
| Constipation | 8.3 (25.8) | -9.3 (24.6) |
| Diarrhea | 27.1 (27.8) | 1.3 (29.6) |
| Financial difficulties | -2.1 (8.3) | -4 (17.5) |

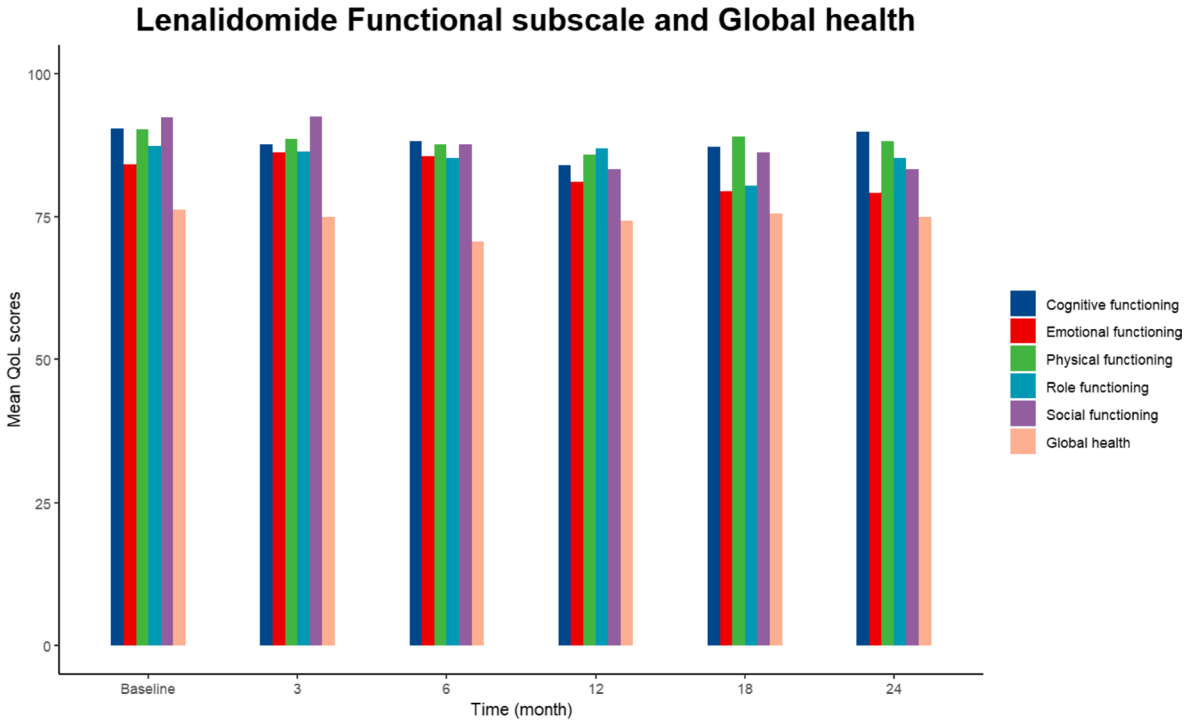
Values that decreased are in bold. This means deterioration on the functional subscale and improvement on the symptom subscale

## Discussion

This Qol of life study shows that lenalidomide supplementation as a consolidation regimen in CLL patients in clinical response but with detectable residual disease has little effect on global health, functional and symptom scores, over the first year of lenalidomide consolidation treatment. However, after the 12-month time point, lenalidomide gradually led to a worsened status compared to patients on observation. Interestingly, in the OBS group there was a gradual improvement of HRQoL parameters over time, as the distance from therapy increased. The response rate in QoL studies is a real challenge. In clinical trials, careful selection of eligible patients and quality of follow-up can increase the response rate. Our study showed a decrease in response rate at each follow-up point in both arms. In the lenalidomide arm, the response rate at 24 months was 56%. The worsening effects of lenalidomide may explain this rate, but the mixed model in data analysis considers the pattern of responders during follow-up to limit potential bias. Despite these effects, lenalidomide treatment in patients with detectable residual leukemia helped to maintain better disease control [12] and significantly improved progression-free survival [11].

This HRQoL study thus mostly provides an objective image of the opposite impact of ongoing therapy and observation ("wait and watch") in this cohort, with a significant increase in diarrhea from month 12 on, and of dyspnea in the late period of the study (months 18 and 24) for patients in the LEN arm. This is consistent with

**a Lenalidomide arm**




**b Observation arm**

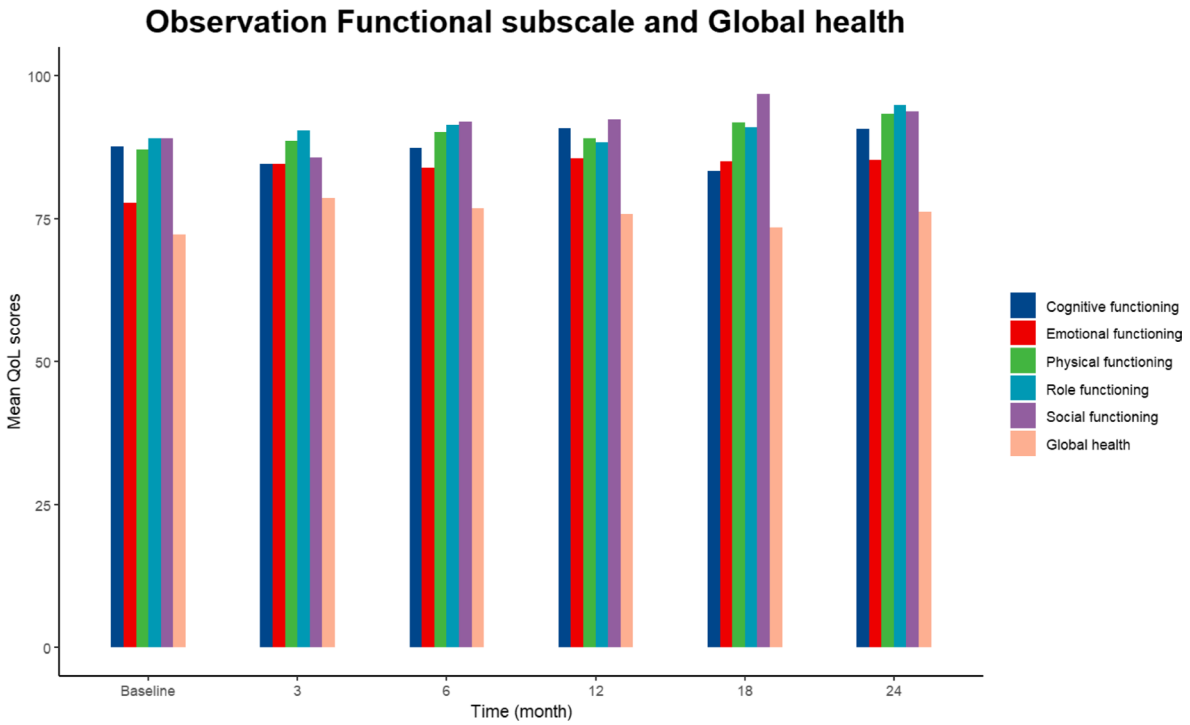



**Fig. 2** Graphical representation of changes in HRQoL functions and global health over time

the higher incidence of leukopenia and respiratory infections in the LEN arm already reported in this trial [13].

The effect of lenalidomide therapy on HRQoL has mostly been examined in the literature in cohorts of multiple myeloma patients, usually showing a good tolerance [14, 15]. Nielsen et al. [14] however noted, as here, an increase in episodes of diarrhea. A study in diffuse large B cell lymphoma reported no negative impact of lenalidomide compared to a placebo arm [16]. This conclusion was drawn from the observation that scores did not change by more than 10 points. However, close examination of the data quasi systematically indicate less improved scores in the LEN arm with a significantly poorer GHS at month 12. Of note, diarrhea was worse in the lenalidomide arm at cycles 12 and 24 in the CLL6-RESIDUUM study reported here.

Outside consolidation therapy, HRQoL questionnaires have been applied in several series of CLL patients. This confirmed in most cases the burden of the disease not only through fatigue and sleep disorders but also on mental functions such as anxiety. The most significant improvement upon treatment was less fatigue. Here, the comparison of baseline and month 24 data in the two populations of patients in CR/PR showed an almost significant improvement of fatigue (-9.5) in the OBS group and virtually no change in the LEN group.

The report of the GIBB study, that used first-line immunochemotherapy with 27 months follow-up, also found improvement of HRQoL, dramatic at month 3 yet followed by global stability [17]. The baseline values reported in the GIBB study, relative to pre-treatment, are all worse than those of both the LEN and OBS CR/PR patients here. Yet, the latter are totally comparable to the "response" time point of Danilov et al. [18]. These data comfort the validity of the HRQoL results reported here for the RESIDUUM trial. This HRQoL study indicates that supplementation with lenalidomide as consolidation therapy in CR/PR CLL, although it controls MRD [11] and improves PFS [10] leads to health deterioration, especially during the second of the two-year period of treatment, compared to off-therapy patients. Since these deleterious effects only become significant after 12 months, such a supplementation could be considered for just one-year post-chemoimmunotherapy, or for 24 months in all but in a discontinued fashion allowing for some washout.

This study presents some limitations by the relatively small size of the cohort and the usual loss of information over time. The data from Australian cohort will increase the sample and would improve the statistical power of the study. Furthermore, the loss of follow-up overtime does not affect the quality of the results because the mixed model was adjusted on the pattern of follow-up patients. Moreover, no HRQoL questionnaires were proposed to the patients after the end of the study, since patients in the LEN arm might have recovered from the drug side effects.

## Conclusions

This study assessed the positive therapeutic effect of lenalidomide consolidation after effective immunochemotherapy, despite a significant late alteration of HRQoL. Another interesting finding is the progressive improvement of QoL parameters in CLL patients off-therapy, even when MRD was still detectable at observation onset. This work ultimately provides HRQoL values in a French cohort of CLL patients in consolidation treatment.

#### Abbreviations

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|---|---|
| HRQoL | Health-Related Quality of Life |
| CLL | Chronic Lymphocytic Leukemia |
| LEN | Lenalidomide Arm |
| OBS | Observation Arm |
| IMiD | Immunomodulating drug |
| IL | Interleukin |
| MRD | Measurable Residual Disease |
| CR | Complete Respon,se |
| PR | Partial Response |
| ICT | Immunochemotherapy treatment |
| FCR | Fludarabine, Cyclophosphamide and Rituximab (FCR) |
| ALLG | Australasian Leukaemia and Lymphoma Group |
| FILO | French Innovative Leukemia Organization |
| PRO | Patient-Reported Outcomes |
| PFS | Progression Free Survival |
| EORTC | European Organization for Research and Treatment of Cancer |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |

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#### Authors' contributions

Conceptualization: MM, TA-S; Methodology: MM, TSD, SKW; Software: SKW; Validation: SKW, FC, TA-S; Formal analysis: SKW, TSD; Investigation: TA-S; Resources: DG, SM, TA-S; Data Curation: SKW; Writing—Original Draft: SKW, TA-S; Writing—Review & Editing: SKW, TSD, DG, FC, SM, MM, TA-S; Visualization: SKW; Supervision: MM, TA-S; Project administration: DG, SM, TA-S; Funding acquisition: MM.

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#### Data availability

Yes, the dataset is available from the first author upon reasonable request.

### Declarations

#### Ethics approval and consent to participate

The protocol was approved by the French National Competent authority (Agence Nationale de Sécurité du Médicament, Reference: 131618A-11) and an Ethics Committee (CPP de Sud Méditerranée I, Reference: 14 05). The study was performed according to the principles of the Declaration of Helsinki. All patients provided written informed consent to participate.

#### Consent for publication

Not applicable.

**Competing interests**
The authors declare no competing interests.

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