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RESEARCH ARTICLE

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Patient-reported outcomes among patients with mantle cell lymphoma or chronic lymphocytic leukemia receiving pirtobrutinib in the BRUIN phase 1/2 study: final analysis

Catherine C. Coombs[a], Jennifer A. Woyach[b], Jennifer R. Brown[c], Paolo Ghia[d,e], Lindsey E. Roeker[f], Krish Patel[g], Toby A. Eyre[h], Constantine S. Tam[i], John F. Seymour[j], Nirav N. Shah[k], Ian Flinn[l], Chan Y. Cheah[m], Shuo Ma[n], Joanna M. Rhodes[o], Koji Izutsu[p], Wojciech Jurczak[q], William G. Wierda[r], Lisa M. Hess[s], Naleen Raj Bhandari[s], Angely Loubert[t], Paolo B. Abada[s] and Nicole Lamanna[u]

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ABSTRACT

Background: This study presents patient-reported outcomes (PROs) from the phase 1/2 BRUIN (NCT03740529) trial of pirtobrutinib monotherapy for the treatment of B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL).

Methods: PROs were collected at each cycle using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and item library (IL) sets for CLL/SLL- and MCL-related symptoms and an Expanded Fatigue measure. Prespecified analyses included descriptive change from baseline, time to worsening (TTW) using Kaplan-Meier method, and longitudinal analyses using a mixed model for repeated measures.

Results: A total of 263 patients with CLL/SLL and 124 with non-blastoid MCL who received pirtobrutinib monotherapy after prior BTKi were included in the final PRO analysis. The proportion of patients with CLL/SLL who improved or remained stable from baseline through Cycle 31 remained above 80% for physical function (PF), CLL/SLL-related symptoms, fatigue, and global health status/quality of life (GHS/QoL). The proportion of patients with MCL who improved or remained stable through Cycle 20 remained above 70% for PF, MCL-related symptoms, fatigue, and GHS/QoL. Median TTW was not reached in either CLL or MCL. Longitudinal analyses for PF, CLL/SLL-related symptoms, fatigue, and GHS/QoL consistently met statistically significant and clinically-meaningful improvement from baseline for CLL. PRO assessments remained stable over time for MCL.

Conclusions: The final analysis from the BRUIN trial demonstrates stability in PROs throughout the duration of treatment with pirtobrutinib. Most patients with CLL/SLL and MCL reported stable or improved outcomes throughout the study.

PLAIN LANGUAGE SUMMARY

This study presents the final analysis of patient-reported outcomes (PROs) from the phase 1/2 BRUIN trial (NCT03740529) investigating pirtobrutinib monotherapy for the treatment of B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL). PRO instruments were collected using paper forms at each patient visit to the study site. This study found that throughout treatment with pirtobrutinib, more than 80% of patients with CLL reported maintained or improved physical function, CLL/SLL-related symptoms, fatigue, and global health status/quality of life. More than 70% of

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b-cell lymphoma; leukemia; pirtobrutinib; quality of life; patient-reported outcomes; clinical trial; physical function

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patients with MCL reported maintained or improved outcomes on similar measures. Overall, this final analysis of data from the BRUIN trial demonstrates stability in PROs throughout the duration of treatment with pirtobrutinib for both patients with CLL and those with MCL.

Introduction

BRUIN (NCT03740529) was an open-label, multi-center phase 1/2 study that investigated the safety and efficacy of pirtobrutinib as monotherapy for the treatment of B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL, hereafter simply CLL), or non-Hodgkin's lymphoma, including mantle cell lymphoma (MCL). Pirtobrutinib is a highly selective, non-covalent Bruton tyrosine kinase inhibitor (BTKi) that received U.S. Food and Drug Administration full approval on December 3, 2025 for the treatment of patients with CLL or SLL who have been previously treated with a covalent BTK inhibitor (cBTKi) and has accelerated approval based on the BRUIN trial for adults with relapsed/refractory MCL after at least two lines of systemic therapy, including a BTKi (January 2023). BRUIN trial results showed median progression-free survival (PFS) of 28.4 months for CLL (not reached for patients with MCL)[1,2].

Subsequently, the confirmatory phase 3 trial (BRUIN CLL-321) met its study endpoints demonstrating the efficacy of pirtobrutinib for patients with CLL after prior covalent BTKi-based therapy (NCT04666038)[3]. In this randomized trial of patients with CLL/SLL after prior cBTKi therapy, PFS was significantly improved with pirtobrutinib compared to investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab (hazard ratio [HR], 0.54; 95% confidence interval: 0.39–0.75; $p = 0.0002$). Four additional phase 3 trials are in progress, designed to further evaluate the efficacy of pirtobrutinib among patients with CLL (NCT05254743, NCT05023980, NCT04965493) or MCL (NCT04662255).

While clinical efficacy has been demonstrated through the completed clinical trials, it is also important to evaluate the impact of this novel agent on patient experience. Previous interim analyses of patient-reported outcomes (PROs) from a datacut in February 2023 revealed that among patients with CLL, more than 70% of patients in the BRUIN trial maintained or improved physical function, quality of life, and CLL/SLL-related symptoms over the first 24 cycles of pirtobrutinib treatment. Similarly, interim analyses of those with MCL in the BRUIN trial found that >75% maintained or improved physical function, quality of life, and MCL-related symptoms during the first 11 cycles of pirtobrutinib treatment[4]. Subsequently, the phase 3 randomized trial (BRUIN CLL-321) demonstrated that among patients randomized to pirtobrutinib, clinically meaningful improvements in PROs from baseline were observed at all post-baseline assessments through week 25 of the study[5,6]. The subsequent and final analysis of PROs from the Phase 1/2 BRUIN trial was conducted using the final datacut in January 2025, which includes nearly two years of additional follow up since the interim analysis. Secondary endpoints in the BRUIN trial included an investigation of clinical response categories with patient-reported symptoms and physical functioning. Exploratory endpoints evaluated PROs throughout the duration of pirtobrutinib treatment and are reported here with the final analysis of the BRUIN trial.

Methods

The BRUIN trial included a cohort of patients with CLL who had received at least two prior lines of therapy, including a cBTKi-containing regimen, as well as a cohort of patients with non-blastoid MCL after prior cBTKi-based therapy. Details of the study design and cohort enrolled to this trial are published elsewhere[7]. The BRUIN study protocol was approved by the institutional review boards or independent ethics committees overseeing each participating clinic site (supplemental content). The study was done in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. All patients provided written informed consent.

There were two PRO-related secondary endpoints in the BRUIN trial for patients with MCL[1]: to determine the association of clinical tumor response categories with improvement in cancer-related symptoms; and[2] to determine the association of clinical tumor response categories with improvement in physical functioning. Similar endpoints evaluating these associations were included in the trial as exploratory endpoints for patients with CLL. Exploratory endpoints also included descriptive analyses of change in PROs from baseline, time to worsening (TTW), and longitudinal analyses of PROs throughout the treatment period. All endpoints and analyses presented in this work were pre-specified in a PRO statistical analysis plan.

PRO instruments

Study endpoints were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30). The QLQ-C30 includes five functional assessment scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/quality of life (GHS/QoL) scale, and six single items assessing other symptoms commonly reported by patients with cancer. All scores are recorded from 0 to 100. Higher scores represent better physical functioning and better GHS/QoL, whereas higher scores represent worse symptoms for CLL/SLL- and MCL-related symptoms and fatigue.

Cancer-related symptoms were evaluated using MCL-related symptom and CLL/SLL-related symptom scales, which were derived from the EORTC Item Library (IL) sets[8]. The MCL-related symptom scale (IL88) was derived including items of nausea, fatigue, general pain, and lack of appetite from the QLQ-C30, items assessing night sweats, fever/chills, and fatigue items from the IL63. The CLL/SLL-related symptom scale (IL87) was derived from 13 items in the IL87 set (QLQ-30 items of dyspnea, fatigue, general pain, sleep problems, lack of appetite, and nausea; as well as IL58 items of night sweats, fever/chills, and additional fatigue items). Additionally, an expanded measure of fatigue was evaluated that combined the fatigue items from the QLQ-C30 along with the fatigue items from the IL58 or IL63 item sets included in the cancer symptom scales. The development and psychometric properties of these instruments have previously been reported[8,9].

Timing of PRO assessments

All PRO instruments were collected using paper forms at each patient visit to the study site, starting at Cycle 1 Day 1 (baseline) prior to study drug administration. PRO assessments were planned to occur at each treatment cycle (approximately at 28-day intervals) throughout the study treatment period. The implementation of the BRUIN trial corresponded with the COVID-19 epidemic, and clinic visits were reduced, resulting in patient visits at approximately every other cycle of treatment or as needed for care. Given the range of timing of PRO assessments, the analysis plan defined windows for clinic visits that were assigned for both scheduled and unscheduled visits to ensure the PRO data analyzed would be consistent across all patients enrolled to the study. Date of PRO completion was assigned a cycle number, with the allowable window corresponding to the date of the start date of the treatment cycle to the day immediately prior to the subsequent cycle start date.

Statistical methods

The relationship between clinical tumor response categories of complete response, partial response, stable disease, and progressive disease was summarized descriptively by PRO response, defined by prespecified clinically meaningful within-patient change thresholds (i.e. the smallest amount of change that would be considered meaningful to an individual patient) in physical function, CLL/SLL- and MCL-related symptoms, and fatigue (Table 1). Meaningful-change thresholds for improvement were assessed based on analysis of blinded data from BRUIN and were further confirmed on combined blinded trial data in patients with CLL and MCL, while those for worsening were based on published recommendation thresholds for EORTC QLQ-C30[10,12]. For patients with CLL, additional categories of complete response with incomplete bone marrow recovery, nodular partial response, and partial response with lymphocytosis were evaluated. Tumor response categories were collapsed to correspond to the assessment of best overall response rate (ORR) reported in the trial[3]. Patients who had improved physical function, symptoms, or fatigue were defined as patients whose change in score from baseline was greater than the meaningful within-patient improvement threshold at the time of tumor response assessment. Sensitivity analyses were conducted describing tumor response categories with PRO response at any time during the study.

Table 1. Thresholds of minimal clinically important difference (MCID).

Instrument	Descriptive and time to event analyses, patient-level changes from baseline		Longitudinal analyses
	Threshold for meaningful improvement[10]	Threshold for meaningful worsening[10]	Threshold for meaningful improvement (group-level change)[11]
CLL/SLL-related Symptoms[12]	−15.38	+10.25	−4.0
MCL-related Symptoms[12]	−10.25	+10.25	−4.0
Fatigue[12]	−16.66	+11.11	−4.0
Physical function	+13.33	−13.33	+2.0
Global health status/quality of life	+16.66	−16.66	+5.0

The proportion of patients who improved, remained stable, or worsened from baseline, based on their individual change, were described at each cycle of treatment for physical function, CLL/SLL- and MCL-related symptoms, fatigue, and GHS/QoL using pre-specified meaningful within-patient change thresholds (Table 1)[12].

Time to worsening (TTW) was evaluated using a Kaplan-Meier approach for physical function, CLL/SLL- and MCL-related symptoms, fatigue, and GHS/QoL. Events were defined as the first observation of worsening that was sustained through at least one subsequent assessment or patient death, whichever occurred first. Worsening in each PRO endpoint was defined based on the same pre-specified clinically meaningful within patient change thresholds as the descriptive analyses (Table 1). Patients without events were censored at their last observed study clinic visit. As a sensitivity analysis, these analyses were replicated estimating time to first deterioration (TTFD) using all participants as well as excluding those who could not worsen from baseline.

Mixed model for repeated measures (MMRM) analyses were used to estimate change in PRO scores from baseline (least square means [LSM]) over time. The response variable was the change in score from baseline at each post-baseline visit and the explanatory variables were time from baseline (study visit), with post-baseline visits (included as a categorical variable) as a fixed effect, baseline score as a covariate, and the individual patient as a random effect. A compound-symmetric covariance structure was used (as the model did not converge with an unstructured covariance structure). Change from baseline (LSM at each study visit) was interpreted following published guidelines for within-group changes based on EORTC QLQ-C30 scores (Table 1), which represent the smallest improvement that is considered clinically relevant at the population level[11].

All analyses were conducted by a third-party research organization (Allucent) using SAS 9.4, with statistical significance defined as $p < 0.05$ (nominal p-values, not controlled for alpha risk). All analyses were descriptive in nature, and no adjustments for multiplicity of testing were conducted. The data cutoff for this final analysis was 27 January 2025.

Results

Study cohorts

There were 263 patients with CLL who had prior cBTKi exposure included in the final analysis with a median (interquartile range [IQR]) follow-up of 46.5 months (35.5, 54.7) from study enrollment. At the time of the data cutoff for this analysis, 39 patients with CLL remained on study (Figure 1). Detailed characteristics of this cohort are published elsewhere[7]. Baseline PRO completion among patients with CLL was 82.1%. Data were available for the most patients with CLL at alternating visits until Cycle 31, at which point only 95 patients (36.1% of those enrolled) remained on study treatment.

There were 124 patients with non-blastoid MCL included in the final PRO analysis with a median (IQR) follow up on study of 39.7 months (IQR: 27.8, 45.0). At the time of the data cutoff for this analysis, 9 patients with MCL remained on study (Figure 1). Detailed

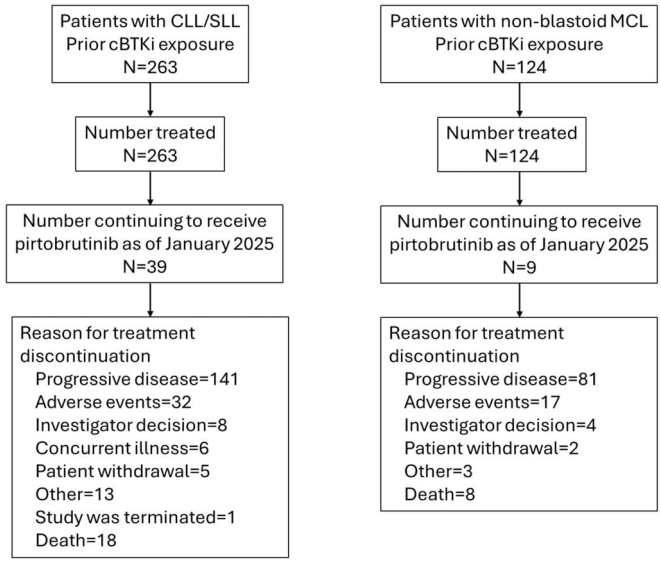


Figure 1. Patient disposition on the BRUIN phase 1/2 trial as of January 2025.

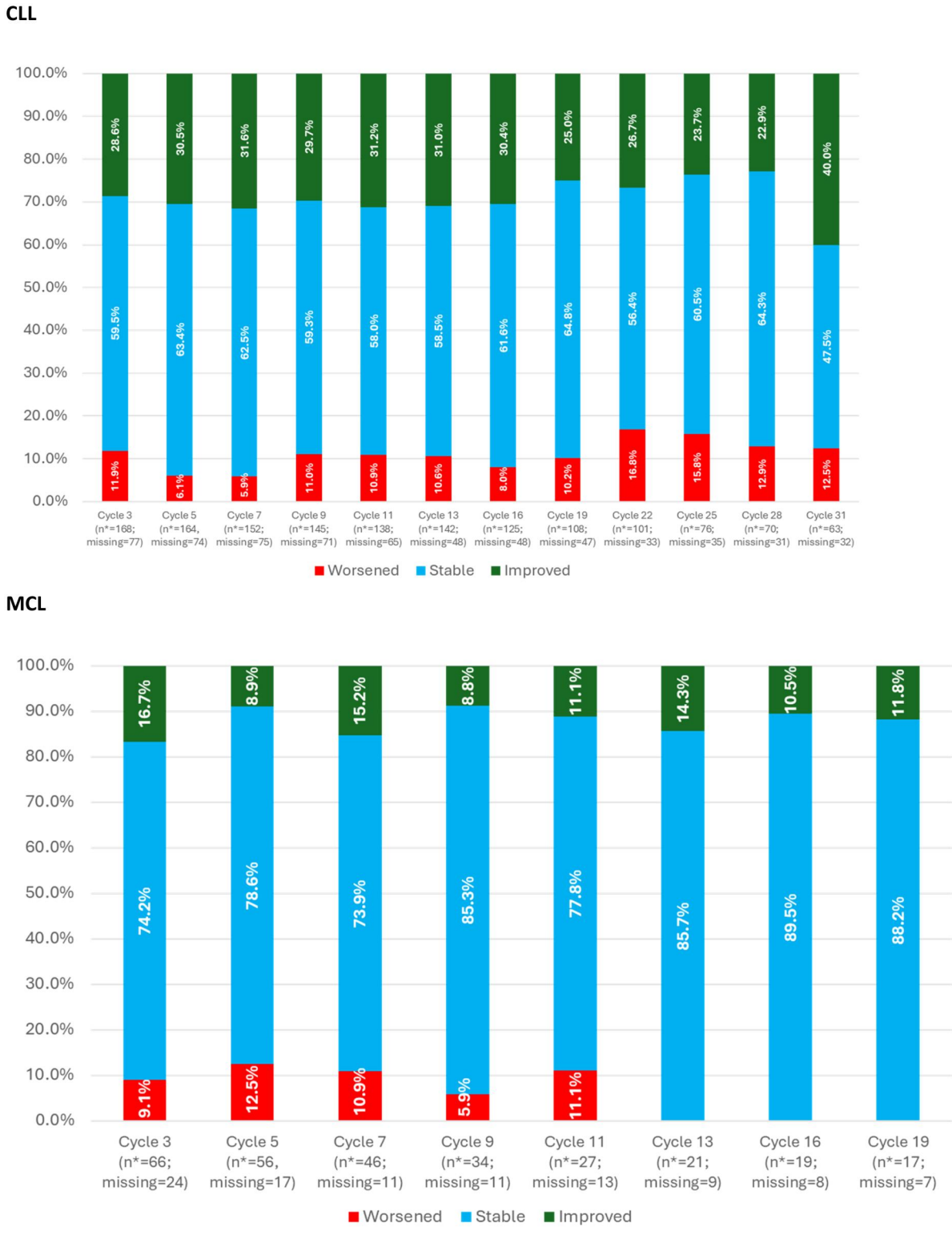


Figure 2. Categories of clinically-meaningful change from baseline in physical function, by clinic visit.
n* = number of evaluable patients.

characteristics of this cohort are published elsewhere[7]. Only 23 patients (18.5%) remained on study by Cycle 20; PRO data are not reported after this point in time as patients were no longer on study to permit data collection. PRO data were considered evaluable for those visits where more than 65% of patients remaining on study completed PRO instruments; visits with high missingness were considered unevaluable. Patterns of missingness were largely due to the timing of this study, which coincided with the COVID-19

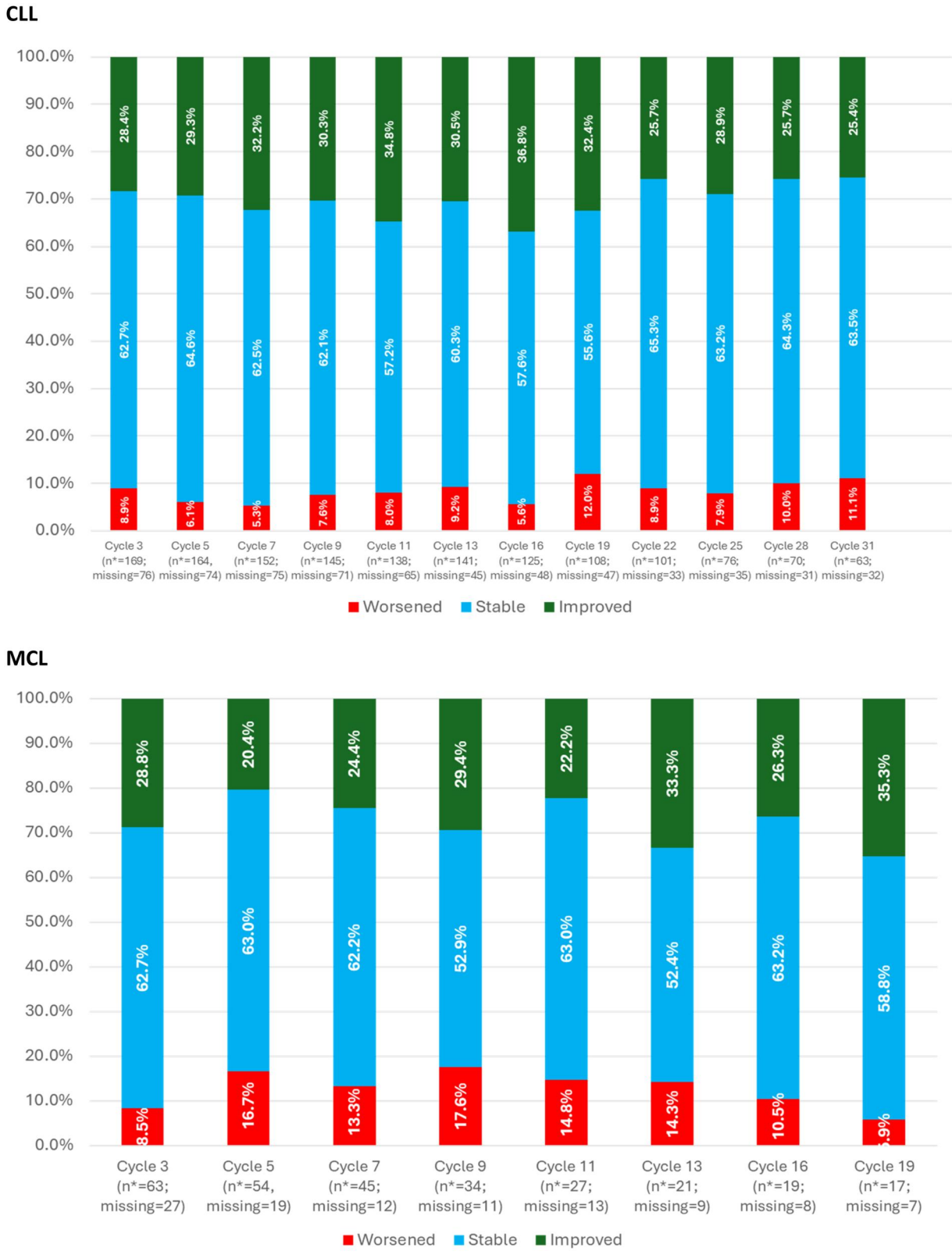


Figure 3. Categories of clinically-meaningful change from baseline in CLL/SLL or MCL-related symptoms, by clinic visit.
n* = number of evaluable patients.

pandemic. To reduce contact between individuals, patient visits to the clinic were reduced, limiting the ability for study participants to complete the paper forms used for PRO data. Furthermore, the patterns of in-clinic visits were inconsistent, leading to completion of forms that were not within similar time windows

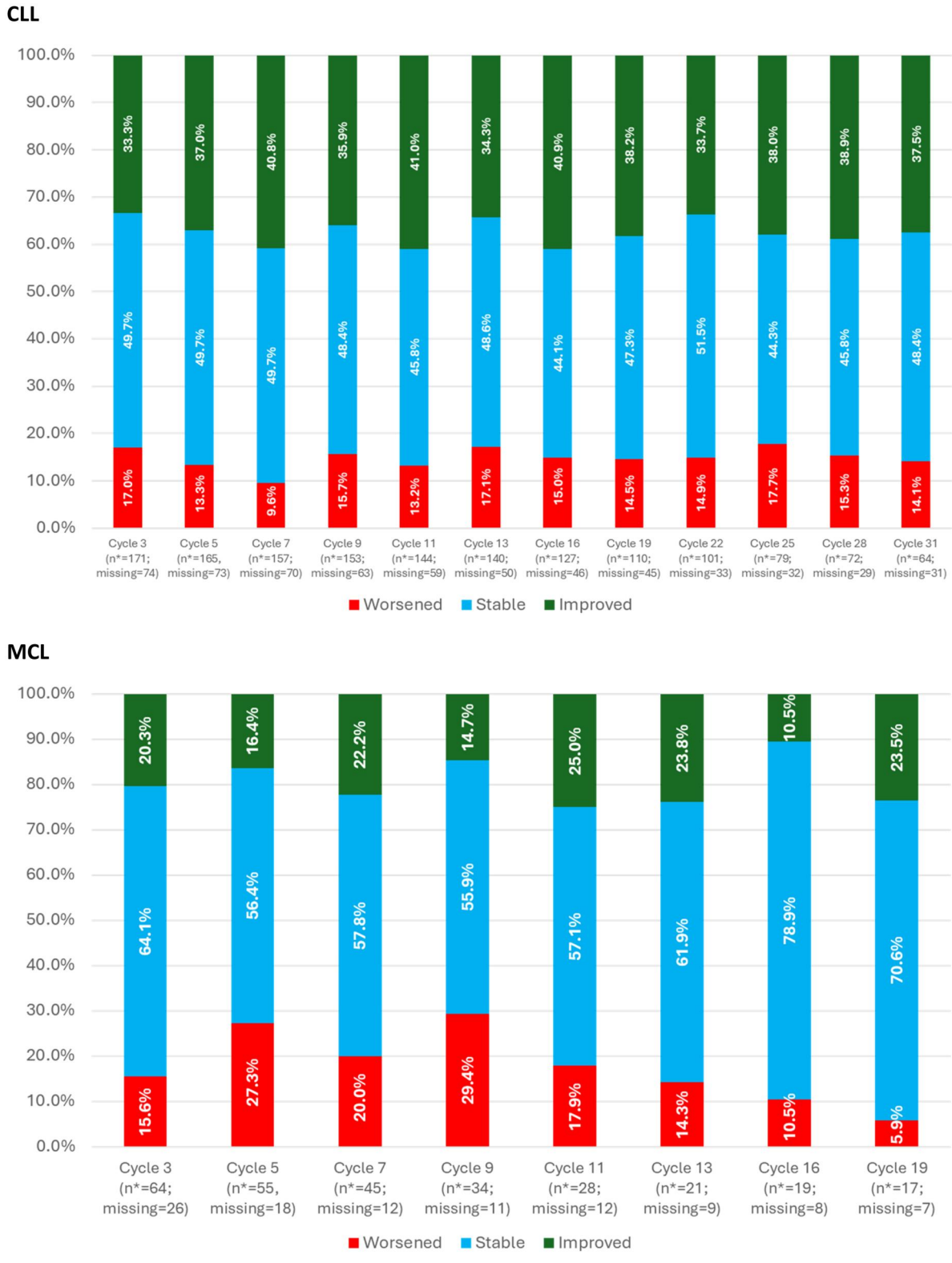


Figure 4. Categories of clinically-meaningful change from baseline in fatigue, by clinic visit.
n* = number of evaluable patients.

for analysis. Therefore, only visits where the majority of patients provided data were used, as the remaining particpants tended to complete paper forms on visits when fewer patients attended the clinic in person.

Descriptive PRO data

For the CLL cohort, the baseline mean score was 80.8 (standard deviation [SD] = 19.5) for physical function, 24.7 (SD = 18.4) for CLL/SLL-related symptoms, 33.4 (SD = 24.7) for fatigue and 61.6 (SD = 23.2) for

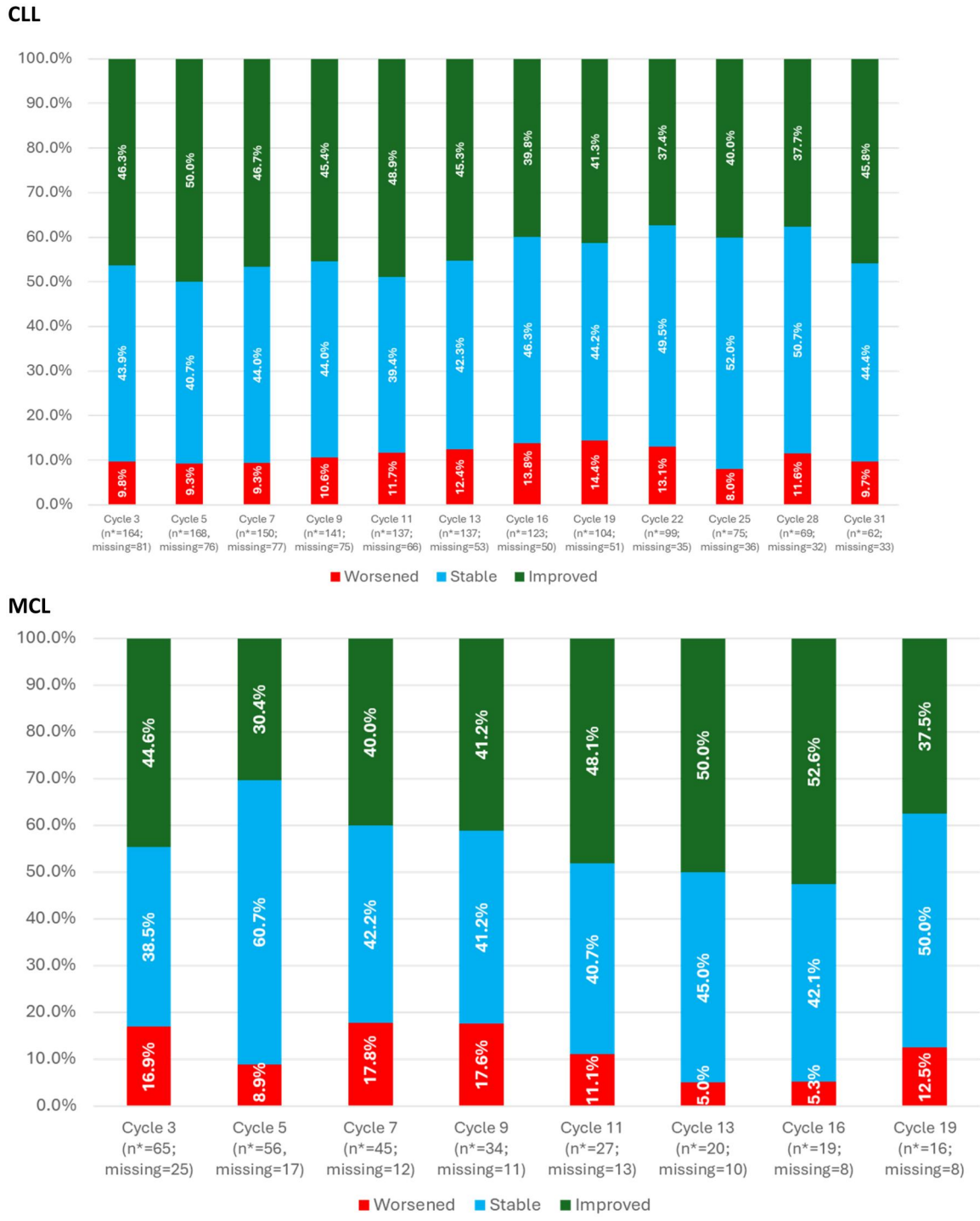


Figure 5. Categories of clinically-meaningful change from baseline in global health status/quality of life by clinic visit.
n* = number of evaluable patients.

GHS/QoL. For MCL, baseline mean scores were 83.6 (SD = 18.0) for physical function, 21.2 (SD = 17.7) for MCL-related symptoms, 29.4 (SD = 23.3) for fatigue, and 62.6 (SD = 23.4) for GHS/QoL.

Most patients with CLL and MCL reported stable or clinically improved PROs at each of the evaluable post-baseline visits. The proportion of patients with CLL who improved or remained stable from baseline through Cycle 31 ranged from 83.1 to 94.1% for physical function, 88.0 to 94.7% for CLL/SLL-related symptoms, 82.3 to 90.5% for fatigue, and 85.6 to 92.0% for GHS/QoL (Figures 2 to 5). The proportion of patients with MCL who improved or remained stable from baseline through Cycle 20 ranged from 87.5 to 100.0%

Table 2. Change from baseline in patient-reported outcomes by tumor response categories for patients with CLL.

	Complete/ partial response $N = 200$	Stable disease $N = 47$	Progressive disease $N = 8$	Tumor response not evaluable $N = 8$
PRO assessment at the time of tumor response				
Physical function, n (% of tumor response category)				
Improvement	40 (30.5%)	6 (16.7%)	0 (0.0%)	0
No improvement	91 (69.5%)	30 (83.3%)	3 (100.0%)	0
Missing	69	11	5	8
CLL/SLL-related symptoms, n (% of tumor response category)				
Improvement	42 (32.1%)	7 (19.4%)	0 (0.0%)	0
No improvement	89 (67.9%)	29 (80.6%)	3 (100.0%)	0
Missing	69	11	5	8
Fatigue, n (% of tumor response category)				
Improvement	59 (43.1%)	8 (22.2%)	0 (0.0%)	0
No improvement	78 (56.9%)	28 (77.8%)	3 (100.0%)	0
Missing	63	11	5	8
PRO assessments throughout the follow up period[a]				
Physical function, n (% of tumor response category)				
Improvement	78 (49.1%)	15 (38.5%)	1 (25.0%)	0
No improvement	81 (50.9%)	24 (61.5%)	3 (75.0%)	0
Missing	41	8	4	8
CLL/SLL-related symptoms, n (% of tumor response category)				
Improvement	79 (49.7%)	15 (38.5%)	1 (25.0%)	0
No improvement	80 (50.3%)	24 (61.5%)	3 (75.0%)	0
Missing	41	8	4	8
Fatigue, n (% of tumor response category)				
Improvement	99 (61.9%)	15 (38.5%)	1 (20.0%)	0
No improvement	61 (38.1%)	24 (61.5%)	4 (80.0%)	0
Missing	40	8	3	8

Abbreviations. PRO, patient reported outcome; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.
Note: Percentage is calculated for those patients evaluable for both tumor and patient-reported outcome assessment.
[a]Clinically-meaningful improvement was defined as at one or more PRO assessments reaching the threshold for clinically-meaningful improvement at any time during the study.

Table 3. Change from baseline in patient-reported outomes by tumor response categories for patients with MCL.

	Complete/ partial response $N = 61$	Stable disease $N = 22$	Progressive disease $N = 32$	Not evaluable $N = 9$
PRO assessment at time of tumor response				
Physical function, n (% of tumor response category)				
Improvement	6 (14.3%)	1 (5.9%)	3 (17.6%)	0
No improvement	36 (85.7%)	16 (94.1%)	14 (82.4%)	0
Missing	19	5	15	9
MCL-related symptoms, n (% of tumor response category)				
Improvement	14 (35.0%)	4 (25.0%)	2 (12.5%)	0
No improvement	26 (65.0%)	12 (75.0%)	14 (87.5%)	0
Missing	21	6	16	9
Fatigue n (% of tumor response category)				
Improvement	12 (30.0%)	2 (12.5%)	3 (18.8%)	0
No improvement	28 (70.0%)	14 (87.5%)	13 (81.3%)	0
Missing	21	6	16	9
PRO assessments throughout the follow up period[a]				
Physical function, n (% of tumor response category)				
Improvement	14 (28.6%)	2 (10.0%)	6 (30.0%)	0
No improvement	35 (71.4%)	18 (90.0%)	14 (70.0%)	2
Missing	12	2	12	7
MCL-related symptoms, n (% of tumor response category)				
Improvement	20 (40.8%)	5 (26.3%)	5 (26.3%)	0
No improvement	29 (59.2%)	14 (73.7%)	14 (73.7%)	2
Missing	12	3	13	7
Fatigue, n (% of tumor response category)				
Improvement	28 (57.1%)	5 (26.3%)	5 (26.3%)	2
No improvement	21 (42.9%)	14 (73.7%)	14 (73.7%)	0
Missing	12	3	13	7

Abbreviations. PRO, patient reported outcome; MCL, Mantle cell lymphoma.
Note: Percentage within the response category was calculated for those patients evaluable for assessment.
[a]Clinically-meaningful improvement was defined as at one or more PRO assessments reaching the threshold for clinically-meaningful improvement at any time during the study.

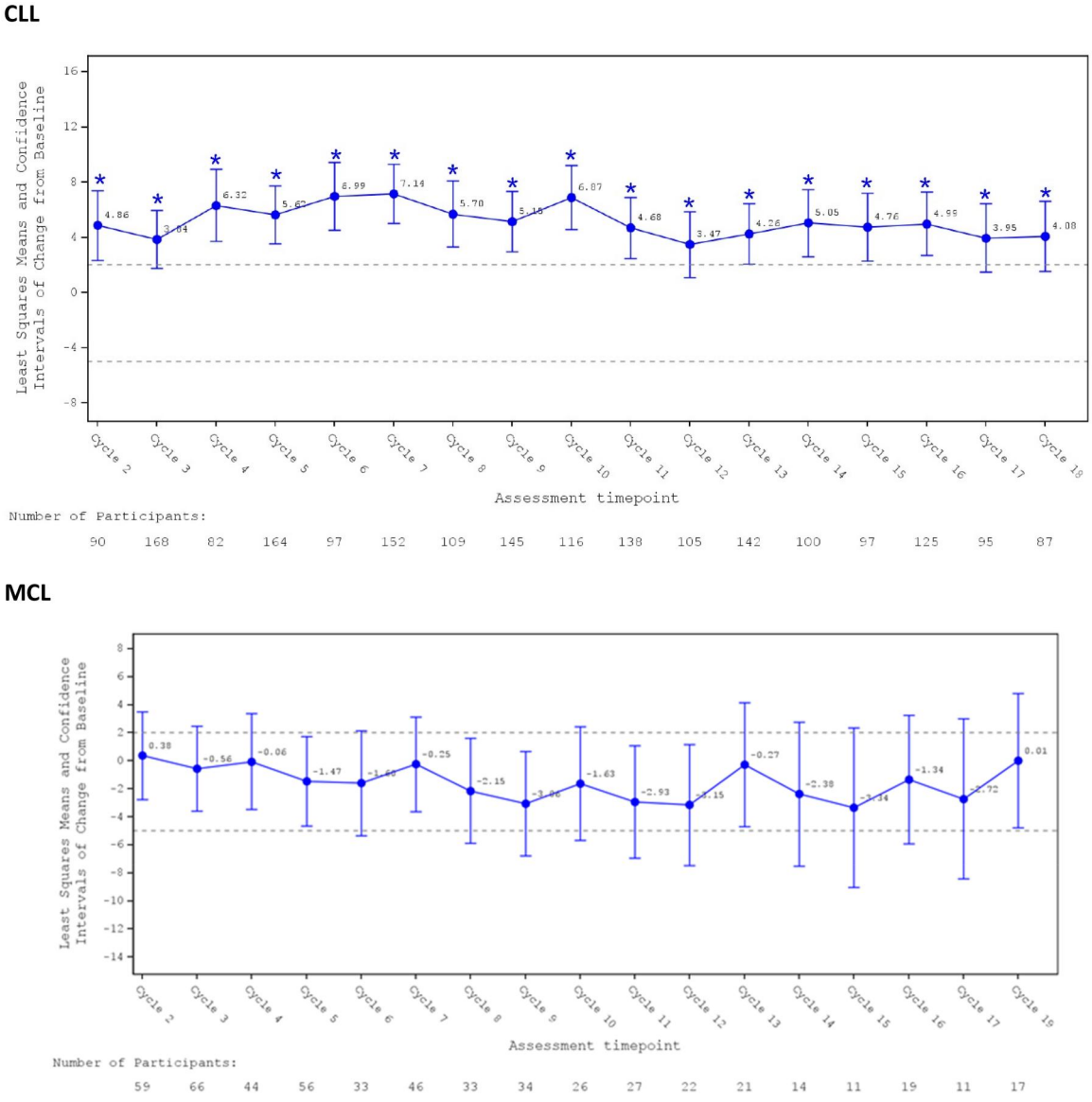


Figure 6. Longitudinal analysis of change from baseline in physical function at each clinic visit.
Note: Upper dotted line represents group-level clinically-meaningful improvement; lower dotted line represents group-level clinically-meaningful worsening; figures presented through Cycle 18 for ease of visualization; the full results are included in Supplementary Materials
*$p < 0.05$ compared to baseline.

for physical function, 82.4 to 94.1% for MCL-related symptoms, 70.6 to 94.1% for fatigue, and 82.2 to 95.0% for GHS/QoL, (Figures 2 to 5).

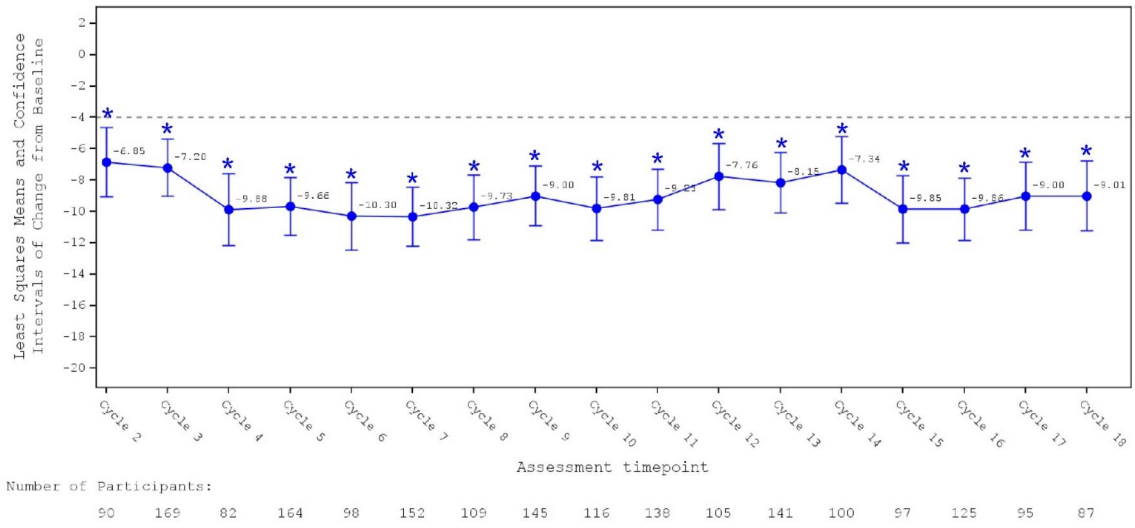
Relationship of clinical tumor response and PRO improvement categories

The proportion of patients who reached a clinically meaningful threshold of improvement in PRO scores at the time of best overall response is summarized in Table 2 (CLL) and Table 3 (MCL). There was no clear pattern in the proportion of patients with PRO improvements either at the time of tumor response or throughout the follow-up period by tumor response category, given the small sample sizes for the stable and progressive disease categories. Sensitivity analyses evaluating PROs at any time during the study did not enhance the ability to interpret these findings (Tables 2 and 3).

Time to worsening of PRO outcomes

Median TTW was not reached for any of the PRO endpoints due to the low rate of PRO worsening or death events among patients treated with pirtobrutinib. For patients with CLL, censoring rates were 76.9% for physical function, 78.8% for CLL/SLL-related symptoms, and 73.0% for fatigue, and 78.1% for GHS/QoL. For MCL, censoring rates were 88.7% for physical function, 87.6% for MCL-related symptoms, 85.7% for fatigue,

CLL/SLL-related symptoms



MCL-related symptoms

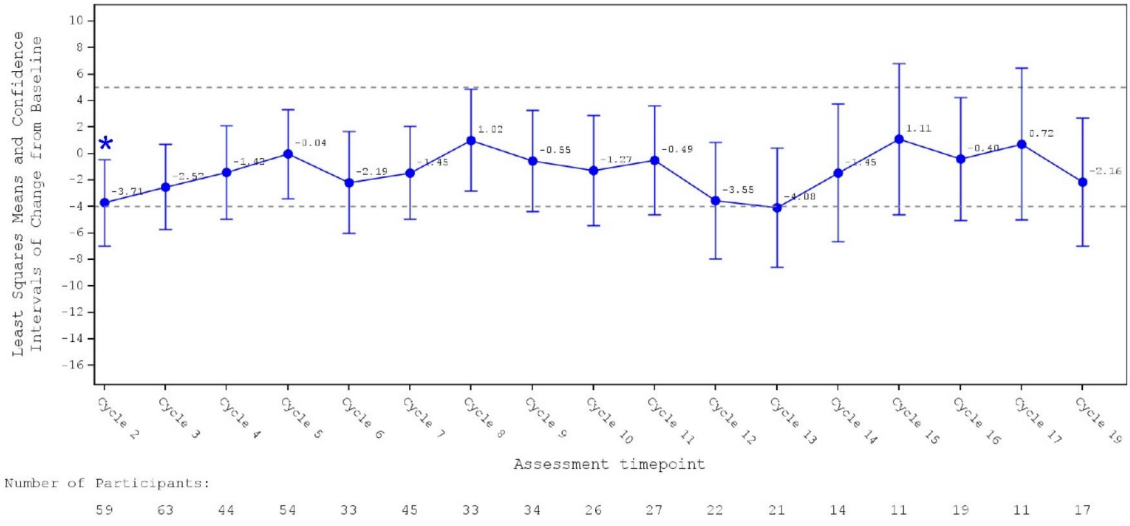


Figure 7. Longitudinal analysis of change from baseline in symptoms at each clinic visit.
Note: Upper dotted line represents group-level clinically-meaningful worsening; lower dotted line represents group-level clinically-meaningful improvement (for CLL, only the improvement line is shown as none of the data reached any worsening value); figures presented through Cycle 18 for ease of visualization; the full results are included in Supplementary Materials
*$p < 0.05$ compared to baseline.

and 84.0% for GHS/QoL. Sensitivity analyses evaluating time to first worsening similarly did not reach a median due to the high levels of censoring; most patients did not experience any worsening event.

Longitudinal analyses

MMRM analyses are presented in Figures 6 to 9. The results of longitudinal analyses demonstrate that physical function consistently met both a clinically meaningful and statistically significant improvement from baseline for patients with CLL through Cycle 31. However, physical function remained stable over time for MCL with no significant differences from baseline; no LSM met a clinically meaningful threshold (Figure 6). Similarly, CLL/SLL-related symptoms consistently met clinically meaningful and statistically significant thresholds for improvement for patients with CLL. MCL-related symptoms were not significantly different from baseline with neither clinically meaningful worsening nor improvement observed for those with MCL over time through Cycle 20, other than at Cycle 2. (Figure 7). Similar patterns were observed for fatigue, where patients with CLL demonstrated statistically significant and clinically meaningful improvements in

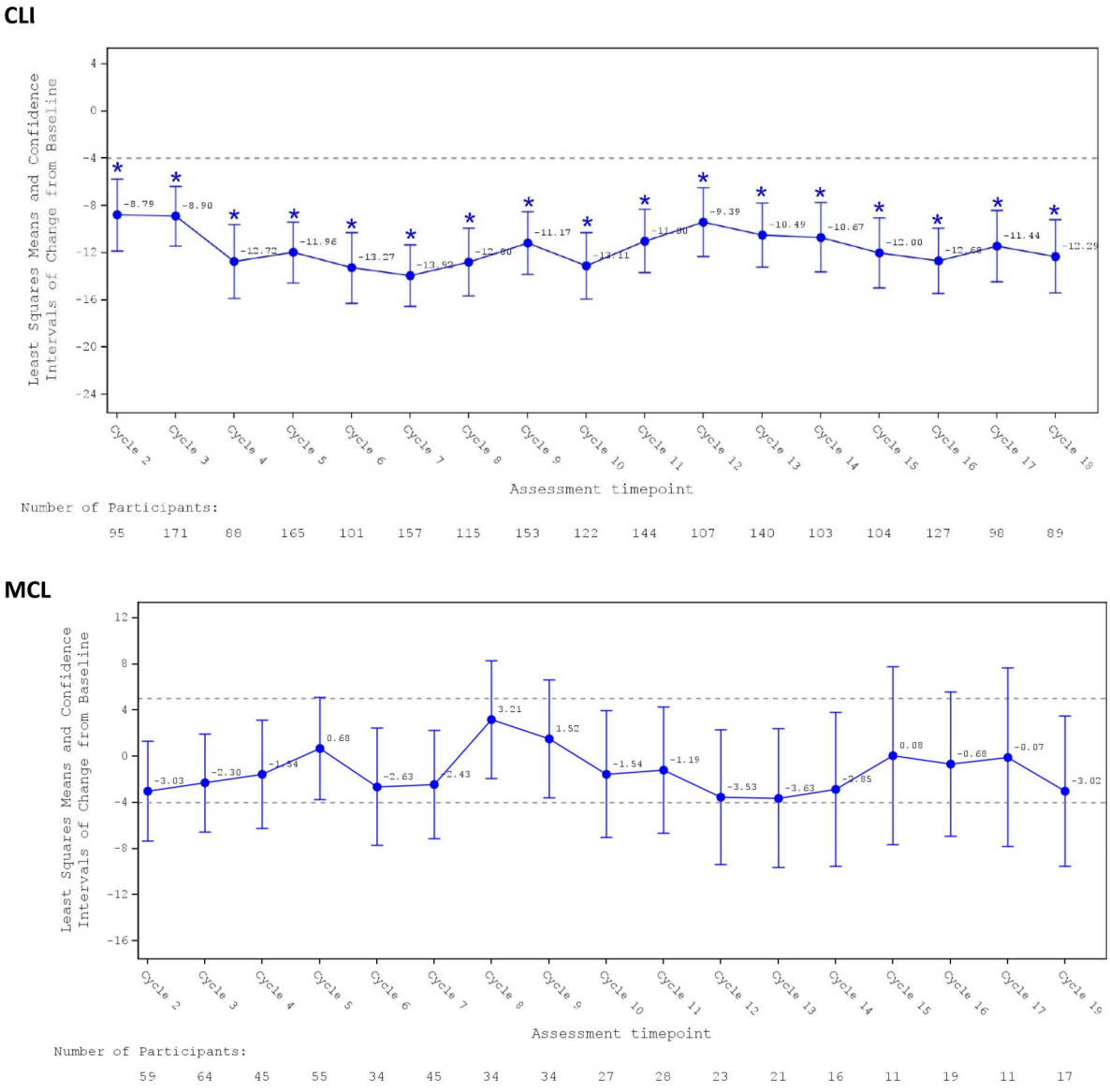


Figure 8. Longitudinal analysis of change from baseline in fatigue over time.
Note: Upper dotted line represents group-level clinically-meaningful worsening; lower dotted line represents group-level clinically-meaningful improvement (for CLL, only the improvement line is shown as none of the data reached any worsening value); figures presented through Cycle 18 for ease of visualization; the full results are included in Supplementary Materials.
* $p < 0.05$ compared to baseline.

fatigue; whereas patients with MCL remained stable over time with no significant or meaningful change observed (Figure 8). GHS/QoL demonstrated consistently statistically significant and clinically meaningful changes from baseline for patients with CLL. This improvement threshold was reached only at Cycles 2 through 5, Cycle 13, and Cycle 16 for patients with MCL, for whom the majority of post baseline GHS/QoL assessments remained stable over time (Figure 9).

Discussion

The final analysis from the BRUIN phase 1/2 trial after an additional 2 years of study follow up continues to demonstrate the stability in PROs throughout the duration of treatment with pirtobrutinib. Treatment with pirtobrutinib in this study achieved a clinically meaningful improvement in PROs among patients with CLL. Patients with MCL remained stable, which remains a favorable outcome in that very few patients experienced any worsening of PRO during study treatment. It is likely that the small sample size in the MCL cohort precluded the identification of mean improvements that met a clinically-meaningful threshold for longitudinal analyses,. The small sample size, combined with the patterns of data collection in the BRUIN trial that led to low rates at some clinic visits, preclude definitive conclusions. Overall, the trends in descriptive

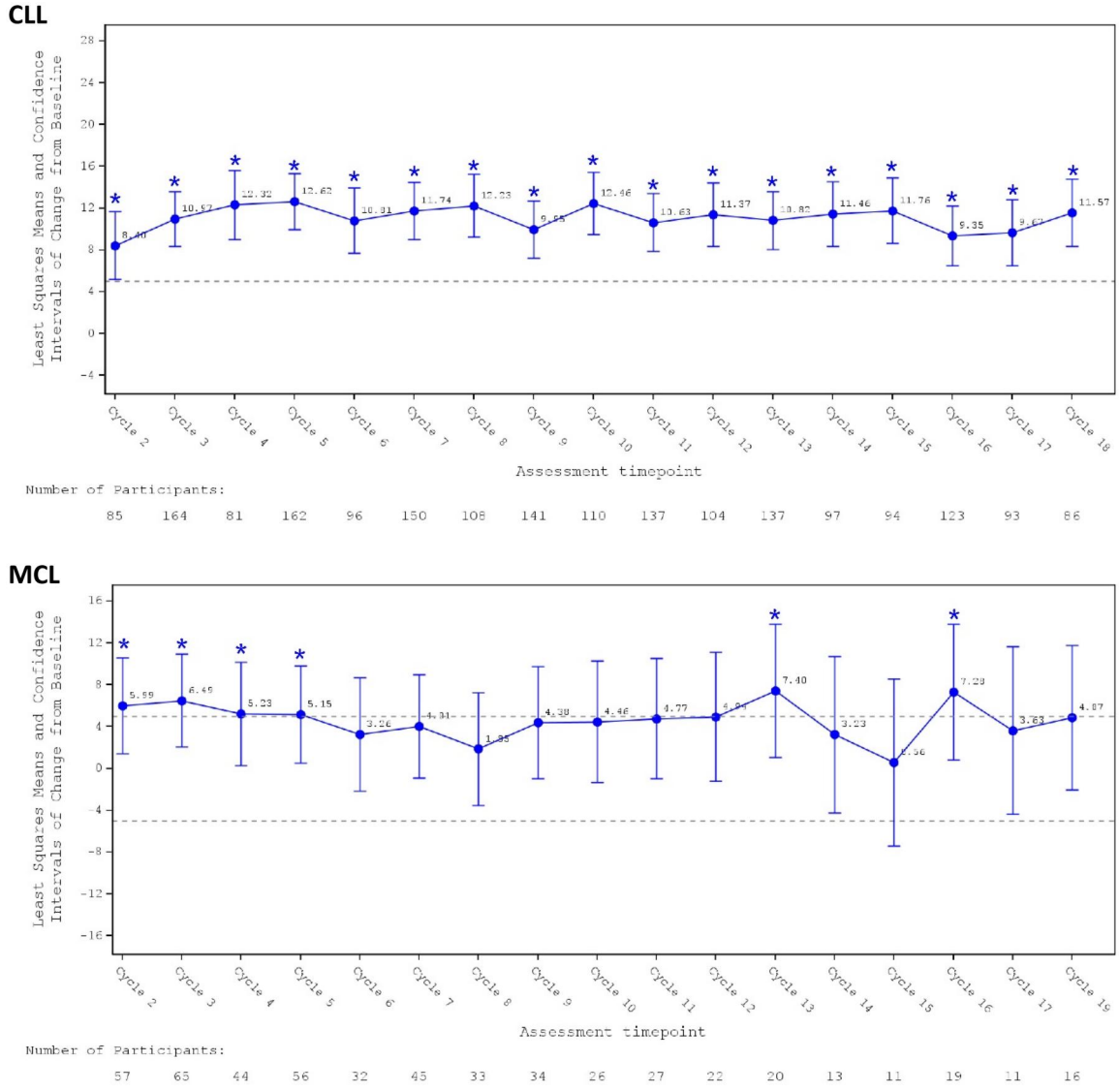


Figure 9. Longitudinal analysis of change from baseline in global health status/quality of life over time.
Note: Upper dotted line represents group-level clinically-meaningful improvement; lower dotted line represents group-level clinically-meaningful worsening (for CLL, only the improvement line is shown as none of the data reached any worsening value); figures presented through Cycle 18 for ease of visualization; the full results are included in Supplementary Materials.
*$p < 0.05$ compared to baseline.

analyses showed similar patterns as CLL in the proportion of patients experiencing stable and improved outcomes, however these results should not be overinterpreted given the limitations of the MCL cohort. Common to all oncology trials, the number of evaluable patients decreases over time as patients discontinue study treatment, as most trials, including BRUIN, only treat patients until disease progression. Therefore, as patients discontinue the study treatment, fewer and fewer patients are available for PRO assessment. After the two-year period, fewer available patients completed the PRO assessments, which limits the interpretation of longer-term outcomes during treatment from this study. This limitation has in part been overcome by the subsequent phase 3 trial, which reports PROs among patients with CLL for a longer period of time[13].

Patients with relapsed/refractory MCL have poor outcomes, particularly after failing covalent BTKi therapy, and the need to maintain quality of life remains central to treatment selection as disease progresses[14]. The ongoing randomized phase III trial of (MCL-321) includes similar PRO endpoints to the BRUIN trial, with an additional endpoint evaluating tolerability of treatment. This trial was designed to enroll 500 patients randomized 1:1 to pirtobrutinib versus investigator's choice of cBTKi monotherapy[15] and has the potential to provide a larger sample that may improve the

ability to evaluate PROs among patients with MCL receiving pirtobrutinib. Further work is needed to understand the relationship of quality of life measures with disease progression, which was limited by the low progression events in this study.

Patients diagnosed with CLL have a five-year survival rate in excess of 85%, which continues to improve as novel therapies and targeted treatment strategies are becoming more widely utilized[16,17]. Because CLL is a chronic disease with the potential of prolonged durations of treatment, the maintenance of quality life is extremely important. Patients with MCL on the other hand, have a five-year survival rate of approximately 50%[18]. Treatment with pirtobrutinib in this study achieved a clinically meaningful improvement in PROs among patients with CLL. The outcomes of PROs were hypothesized to be associated with clinical response outcomes. This study was unable to fully evaluate this hypothesis given the low number of PRO responses across all clinical response categories at the time of tumor assessment. Future research may consider using a wider window of PRO response outcomes to evaluate the trajectory of patient outcomes leading up to broader response categories with a larger patient sample. The data in this study were insufficient to draw definitive conclusions related to this association.

PRO data from other studies are relatively limited for patients with either CLL or MCL. A systematic review of publications from 2018 to 2024 identified 10 trials reporting PROs in CLL[19]. This review found that among trials of lymphoma, leukemia and myelodysplastic syndrome, only about half of identified clinical trials collected PROs at all, and of those that did, barely one-third reported the outcomes in the primary manuscript. A systematic review prior to the publication of the PRO outcomes of pirtobrutinib found only five studies reporting these outcomes among patients with MCL over an 11-year period[20]. This low rate of data generation has led to a gap in knowledge for patients about what to expect while receiving anticancer treatments for these diseases, whether it be CLL or MCL. Preliminary PRO data from the phase 3 trial of pirtobrutinib in CLL as compared to investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab (NCT04666038) support the findings of the BRUIN phase 1/2 PRO analyses presented here[5]. In both the phase 1/2 and phase 3 trials of pirtobrutinib, the majority of patients treated with pirtobrutinib demonstrated stable or improved PROs over time. Trials of first- versus second-generation cBTKi therapy have also shown that for patients with CLL, these targeted cancer therapies also tend to maintain or improve quality of life over time[21].The CLL-314 study (NCT05254743) will evaluate PRO outcomes for the first-generation covalent BTKi, ibrutinib, versus the non-covalent BTKi, pirtobrutinib; however, results for the PRO endpoints are not yet available.

Conclusion

It is imperative that PRO data are collected and disseminated so that patients and their providers can have a complete body of information to inform shared treatment decision making across all therapies available for patient care. The maintenance and improvement of quality of life is extremely important for patients with CLL or MCL. This study adds to the body of knowledge regarding patient experience while receiving pirtobrutinib, and continues to show the stable and improved outcomes that patients can expect following treatment initiation.

Transparency

Declaration of funding

This clinical trial was sponsored by Eli Lilly and Company.

Declaration of financial and other relationships/ conflict of interests

CC receives institutional research funding from Eli Lilly and Co, consulting fees from AbbVie, AstraZeneca, Beigene, Lilly, Genentech, Octapharma, Janssen, BMS, Pharmacyclics, and Allogene, and honoraria from AbbVie, Beigene, AstraZeneca, and Eli Lilly and Co.

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JS serves as consultant for Genor Bio and TG Therapeutics, receives institutional research funding from AbbVie, BMS, and Roche, serves on the speakers' bureau for AbbVie, Astra Zeneca, BMS, and Roche, and receives honoraria from AbbVie, Astra Zeneca, Beigene, BMS, Gilead, Janssen, and Roche.

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LMH, NRB, and PBA are employees of Eli Lilly and Company.

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Data availability statement

Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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References

[1] Shah NN, Wang M, Roeker LE, et al. Pirtobrutinib monotherapy in Bruton tyrosine kinase inhibitor-intolerant patients with B-cell malignancies: results of the phase I/II BRUIN trial. Haematologica. 2025;110(1):92–102. doi: 10.3324/haematol.2024.285754.

[2] Wang ML, Jurczak W, Zinzani PL, et al. Pirtobrutinib in covalent Bruton tyrosine kinase inhibitor pretreated mantle-cell lymphoma. J Clin Oncol. 2023;41(24):3988–3997. doi: 10.1200/JCO.23.00562.

[3] Sharman JP, Munir T, Grosicki S, et al. Phase III trial of pirtobrutinib versus idelalisib/rituximab or bendamustine/rituximab in covalent bruton tyrosine kinase inhibitor–pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma (BRUIN CLL-321). J Clin Oncol. 2025;43(25):2841–2841. doi: 10.1200/JCO-25-01700.

[4] Cohen J, Roeker L, Cheah C, et al. P1112: patient-reported outcomes (Pro) among patients with mantle cell lymphoma receiving pirtobrutinib after prior covalent btki: interim pro analysis from the bruin phase 1/2 study. HemaSphere. 2023;7(S3):e34270c5. doi: 10.1097/01.HS9.0000971344.34270.c5.

[5] Barr PM, Rossi D, Ferrant E, et al. Patient reported outcomes in BRUIN CLL-321: a phase 3 trial of pirtobrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated chronic lymphocytic leukemia/small lymphocytic lymphoma. Value in Health. 2025;28(6):S327. doi: 10.1016/j.jval.2025.04.1411.

[6] Ghia P, Rossi D, Ferrant E, et al. Patient-reported outcomes from BRUIN CLL-321: phase 3 trial comparing pirtobrutinib to idelalisib/rituximab or bendamustine/rituximab in covalent BTKi pretreated CLL/SLL. Hematol Oncol. 2025;43:e219.

[7] Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892–901. doi: 10.1016/S0140-6736(21)00224-5.

[8] Loubert A, Creel K, Hess L, et al. CO115 psychometric evaluation of customized lymphoma-specific symptom measures using the EORTC QLQ-C30 and item library: data from a phase 1/2 clinical trial of pirtobrutinib. Value in Health. 2023;26(6):S36. doi: 10.1016/j.jval.2023.03.188.

[9] Markowitz JT, Mazerolle F, Lovell T, et al. Mixed-methods research to support the use of new lymphoma-specific patient-reported symptom measures derived from the EORTC item library. J Patient Rep Outcomes. 2024;8(1):8. doi: 10.1186/s41687-024-00683-2.

[10] Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139–144. doi: 10.1200/JCO.1998.16.1.139.

[11] Cocks K, King M, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer. 2012;48(11):1713–1721. doi: 10.1016/j.ejca.2012.02.059.

[12] Loubert A, Creel K, Bhandari NR, et al. Psychometric analysis of new lymphoma-specific patient-reported symptom measures derived from the EORTC item library. J Patient Rep Outcomes. 2025; Submitted.

[13] Barr P, Ghia P, Rossi D, et al. 219 | PATIENT REPORTED OUTCOMES FROM BRUIN CLL-321: PHASE 3 TRIAL COMPARING PIRTOBRUTINIB TO IDELALISIB/RITUXIMAB OR BENDAMUSTINE/RITUXIMAB IN COVALENT BTKi PRETREATED CLL/SLL. Hematol Oncol. 2025;43:e219_70094. doi: 10.1002/hon.70094_219

[14] Silkenstedt E, Dreyling M. Treatment of relapsed/refractory MCL. Blood. 2025;145(7):673–682.

[15] Eyre TA, Shah NN, Dreyling M, et al. BRUIN MCL-321: phase III study of pirtobrutinib versus investigator choice of BTK inhibitor in BTK inhibitor naive mantle cell lymphoma. Future Oncol. 2022;18(36):3961–3969. doi: 10.2217/fon-2022-0976.

[16] SEER. The surveillance, epidemiology, and end results (SEER) program of the National Cancer Institute, Cancer Statistics; 2025.

[17] Wagle NS, Nogueira L, Devasia TP, et al. Cancer treatment and survivorship statistics, 2025. CA Cancer J Clin. 2025;75(4):308–340. doi: 10.3322/caac.70011.

[18] Cencini E, Calomino N, Franceschini M, et al. Survival outcomes of patients with mantle cell lymphoma: a retrospective, 15-year, real-life study. Hematol Rep. 2024;16(1):50–62. doi: 10.3390/hematolrep16010006.

[19] Patel K, Ivanov A, Jocelyn T, et al. Patient-reported outcomes in phase 3 clinical trials for blood cancers: a systematic review. JAMA Netw Open. 2024;7(6):e2414425-e. doi: 10.1001/jamanetworkopen.2024.14425.

[20] Monga N, Garside J, Davids MS, et al. Systematic literature review of economic evaluations, costs/resource use, and quality of life in patients with mantle cell lymphoma. Pharmacoecon Open. 2021;5(2):175–186. doi: 10.1007/s41669-020-00231-w.

[21] Tam CS, Lamanna N, O'Brien SM, et al. Health-related quality of life outcomes associated with zanubrutinib versus ibrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: results from the ALPINE Trial. Curr Med Res Opin. 2023;39(11):1497–1503. doi: 10.1080/03007995.2023.2262378.