radiologists and relevant clinical data will be assessed by an independent oncologist. The IRC process will be described in detail in a separate charter.

Table 12: Criteria for Response Categories

Parameter	CR	PR	PD
Group A			
Lymphadenopathy[a]	None >1.5cm	Decrease ≥50%[b]	increase ≥50% or appearance of new lesions >1.5 cm
Hepatomegaly	None	Decrease ≥50%	increase ≥50% or appearance of new hepatomegaly
Splenomegaly	None	Decrease ≥50%	increase ≥50% or appearance of new splenomegaly
Blood lymphocytes	<4000/µL	Decrease ≥50% from baseline	increase ≥50% over baseline[d]
Marrow[c]	Normocellular, <30% lymphocytes, no B lymphoid nodules. Hypocellular marrow defines CRi	50% reduction in marrow infiltrates or B lymphoid nodules	
Group B			
Platelet count	>100,000/µL	>100,000/µL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11 g/dL	>11g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophils[c]	>1500/µL	>1500/µL or increase ≥50% over baseline	

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response with an incomplete marrow recovery; PD = disease progression; PR = partial response

[a] Sum of the products of multiple lymph nodes (as evaluated by CT scans)
[b] Defined as a decrease in lymph nodes of ≥50% either in the sum products of the diameter of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node detected prior to the therapy, as well as no increase in any lymph node and no new enlarged lymph nodes. Note: in small lymph nodes <2 cm, an increase of <25% is not considered to be significant.
[c] This parameter is not relevant for the PD category.
[d] Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other evidence of progressive disease.
Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system
CR: all of the criteria need to be met and subjects have to lack disease-related symptoms.
PR: At least 2 criteria from Group A plus 1 of the criteria from Group B must be met. In all cases, in order for a response to be termed a PR, the blood lymphocyte count should be normalized or decreased >50% from baseline (if elevated at baseline).
NOTE: If only 1 measurable Group A criterion is present at baseline (eg, enlarged lymph nodes but no other abnormality), per recent clarifications of the iwCLL criteria[25,26] these subjects are still considered evaluable for PR if the given parameter improves by at least 50% for a minimum of 56 days. Subjects are also required to have 1 Group B parameter, which can either be improvement in a previously abnormal finding or the persistence of a normal value for at least 56 days as a result of therapy.
PD: at least 1 of the above criteria from Group A or B are met; or transformation to more aggressive histology (eg, Richter's transformation); or a ≥50% increase from the nadir count confirmed on ≥2 serial assessments if the ALC is ≥30,000/µL and lymphocyte doubling time is rapid, unless considered treatment-related lymphocytosis. A new organ infiltrate, bone lesion, ascites, or pleural effusion confirmed due to CLL would also be considered PD.
Reference: modified from 2008 iwCLL criteria[24,25,26]

Complete Response with an Incomplete Marrow Recovery (CRi):

CRi is defined as a complete response with an incomplete recovery of the subject's bone marrow. Subjects who have a CRi fulfill the criteria for a CR, but continue to have persistent anemia, thrombocytopenia, and/or neutropenia, with a hypocellular bone marrow confirmed by bone marrow biopsy. These cytopenias are considered due to drug toxicity in the bone marrow and are not related to CLL.

Nodular Partial Response (nPR):

nPR is a response that meets the criteria for CR, but the bone marrow biopsy shows lymphoid nodules, reflecting residual disease.

Partial Response (PR) with Lymphocytosis:

PR with lymphocytosis is a response where subjects meet the criteria for a PR and have persistent lymphocytosis.

Stable Disease:

Subjects who do not meet the criteria for CR, CRi, nPR, PR, or PD.

Treatment-related Lymphocytosis:

Treatment-related lymphocytosis is defined as an elevation in blood lymphocyte count of ≥50% compared with baseline that occurs in the setting of unequivocal improvement in at least 1 other disease-related parameter, including lymph node size, spleen size, blood counts (hemoglobin and platelet count), or disease-related symptoms. Treatment-related lymphocytosis is isolated lymphocytosis that occurs when no other criteria for PD are met. It will not be considered PD.

9.2.4. Patient-reported Outcomes

PRO assessments will be conducted as described in the Time and Events Schedules. Collection of PRO assessments will stop after the primary PFS analysis is completed.

Three PRO instruments will be administered in this study: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and the EuroQol 5 Dimension 5 Level questionnaire (EQ-5D-5L). The EORTC QLQ-C30 is a 30-item general cancer assessment that incorporates five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status and QoL scale (two items), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores range from 0 to 100 (for functional and global QoL scales, higher scores indicate a better level of functioning). Differences of ≥10 points on EORTC scales are considered clinically important.