Title: Symptoms associated with disease progression in chronic lymphocytic leukemia: achieving expert clinician consensus through an international Delphi panel

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Introduction: Disease progression in chronic lymphocytic leukemia (CLL) is defined using clinical and laboratory criteria set by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL). Progression-free survival (PFS) is considered a key endpoint in oncology trials, however, the patient relevance of PFS as an endpoint is being evaluated by the German Federal Joint Committee (G-BA) among other health technology assessment bodies. While the association between patient-reported outcomes and PFS have been explored, there is no current composite endpoint integrating both measures for use in CLL clinical trials. This study aimed to define symptoms associated with CLL disease progression through consensus among clinicians using a three-round modified Delphi panel.

Methods: To inform the development of the questionnaire, a systematic literature review was conducted to identify published evidence evaluating symptoms associated with CLL and/or disease progression. In addition, key symptoms identified

as patient-relevant by the G-BA were included. The questionnaire was distributed using a modified Delphi panel over three rounds to a total of nine CLL experts from France, Germany, Italy, Poland, the United Kingdom, and the United States. Experts evaluated whether in their opinion the onset or worsening of each symptom was associated with disease progression (as per iwCLL criteria), and the timing of when symptoms were expected to occur relative to disease progression (before, during, or after); consensus was predefined as ≥70% agreement. Following rounds 1 and 2, anonymized aggregate responses were fed back to participants to facilitate consensus.

Results: A total of 13 symptoms were identified from the literature (anxiety/depression, appetite loss, bruising, constipation, diarrhea, dry mouth, dyspnea, fatigue, insomnia, nausea/vomiting, night sweats, pain, weight loss) and three were identified by the G-BA as being patient-relevant (fever, massive splenomegaly, bulky lymphadenopathy). Experts proposed an additional seven symptoms (cough, early satiety/left upper quadrant (LUQ) pain, feeling sick or unwell, headache, peripheral oedema, recurrent sinopulmonary infections, weakness) in round 1. Of these, there was consensus that the onset or worsening of 15 symptoms may be associated with CLL progression (appetite loss, bruising, dyspnea, fatigue, night sweats, pain, weight loss, fever, massive splenomegaly, bulky lymphadenopathy, recurrent sinopulmonary infections, peripheral oedema, weakness, feeling sick or unwell, and early satiety/LUQ pain). Conversely, there was consensus that dry mouth, insomnia, and headache were not usually associated with progression. No consensus was reached on whether the onset or worsening of anxiety/depression, constipation, diarrhea, nausea/vomiting, and cough were associated with disease progression.

Among the 15 symptoms considered associated with disease progression, there was consensus that a specific time window exists for the onset or worsening of seven symptoms (appetite loss, early satiety and/or LUQ pain, feeling sick of unwell, night sweats, recurrent sinopulmonary infections, weakness, weight loss); no consensus was reached regarding the time window of onset or worsening for the remaining eight symptoms. There was consensus among experts for the timing of onset or worsening of 'weight loss' and 'weakness' (within 3 months before disease progression); 'appetite loss' (between 1 and 3 months before disease progression); 'night sweats' and 'recurrent sinopulmonary infections' (within 1 month before progression); 'feeling sick or unwell' (1 month before and up to 1 month after progression), and 'early satiety/LUQ pain' (from 3 to 1 month before progression and up to 1 month after progression).

Conclusions: This modified Delphi panel of international experts reached consensus on the onset or worsening of 15 symptoms associated with CLL progression, as well as on the temporal relationship between seven symptoms and clinical progression. While consensus was not achieved on for the association or timing of symptoms, these findings provide a foundation for defining symptomatic progression in CLL. These results will now be validated among individuals with CLL to confirm the relevance of the findings from a patient perspective. Future work using patient-reported outcome data should evaluate these results in clinical trials.