4.0   Abstract

Title: Cross-sectional Study Evaluating the Effectiveness of the Venetoclax Patient Card Among Adult Patients in Europe

Rationale and Background: Venclyxto (venetoclax), developed by AbbVie and Genentech/Roche, is a first-in-class oral inhibitor of B-cell lymphoma 2 (BCL-2), an anti-apoptotic protein critical to B-cell survival. Venetoclax was initially approved in December 2016 in the European Union (EU) and the United Kingdom (UK) as a monotherapy for the treatment of chronic lymphocytic leukaemia (CLL) in adult patients (European Medicines Agency [EMA], 2016). Venetoclax monotherapy is indicated for the treatment of CLL in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. In 2018, venetoclax was approved in combination with rituximab for adult patients with CLL who have received at least 1 prior therapy and approved in 2020 in combination with obinutuzumab for adult patients with previously untreated CLL. Venetoclax was also approved in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy in 2021.

Tumour Lysis Syndrome (TLS) has been identified as an important risk for patients with CLL treated with venetoclax. Tumour Lysis Syndrome is a known oncology emergency requiring prompt management of metabolic changes to avoid clinical consequences.

The frequency and severity of TLS is largely mitigated through initiation of venetoclax at a 20-mg dose followed by a dose titration schedule that allows for more controlled killing of tumour cells and gradual debulking of the tumour over the titration period. Prophylaxis measures for TLS include hydration and administration of uric acid reducing agents as well as frequent monitoring of blood chemistries and prompt correction of any abnormalities. More intensive measures may be needed as TLS risk increases.

In May 2021, within the context of a type II variation procedure and at the request of the EMA, a patient card (PC) was developed and is being distributed to patients to increase awareness and knowledge of the key messages about the risk of TLS associated with venetoclax. AbbVie agreed to evaluate the effectiveness of the PC through the conduct of a patient survey. The current study is being conducted to evaluate the knowledge and use of the PC for the CLL indication due to the risk of TLS in this population.

Research Question and Objectives: The aims of the study are to evaluate patients' receipt and use of the PC and to assess their knowledge of its contents related to TLS symptoms, patient steps to minimise TLS, and patient actions if TLS symptoms occur.

The primary objectives are as follows:

- To assess patients' knowledge of the following:
  - TLS as a risk of venetoclax treatment for CLL
  - Symptoms of TLS
  - Steps to take to reduce the risk of TLS (e.g., hydration)
  - Actions to take if symptoms of TLS appear
- To assess patients' use of the PC as follows:
  - Whether the patient keeps the PC on their person
  - Whether the PC is shared with all medical providers when seeking care

The secondary objectives are as follows:
- To ascertain when and from whom patients with CLL receive the PC
- To ascertain the number of participating patients with CLL who did not receive and/or do not recall receiving the PC

Study Design: This study will be a cross-sectional survey of knowledge of the risks and safe use of venetoclax as outlined in the PC among adult patients who have recently received venetoclax for treatment of CLL per standard of care. Patients will be identified through a diverse selection of medical practices representing haematologists who prescribe venetoclax across at least 5 European countries.

Patients will be invited to participate by their physician and will be asked to complete a one-time questionnaire at the site on a study-issued tablet computer. Written informed consent will be obtained from each eligible and interested patient before completion of this questionnaire. After giving consent, patients will be asked to complete the questionnaire evaluating their knowledge of various aspects of the PC, such as awareness of TLS as a risk factor for venetoclax treatment for CLL, symptoms of TLS, steps to take to reduce the risk of TLS, and actions to take if symptoms of TLS appear.

Data collection will be initiated in each country several months after the distribution of the PCs is complete in all study countries to allow adequate time for potential survey participants to have received and used the PC as part of venetoclax treatment and to allow time for study preparation activities.

This study is not designed to assess the safety of venetoclax or to solicit adverse events (AEs). The survey does not include questions that would elicit reports of AEs or provide free-text fields in which study participants could provide information on AEs. However, spontaneous AEs may be communicated by participants during the qualitative cognitive pretesting interviews. The process for AEs reporting will be described further in a brief safety reporting plan.

Population: Patients initiating venetoclax for the treatment of CLL in the past 8 weeks will be targeted for participation in the study. Patients will be identified and recruited through clinical sites. Countries are anticipated to include France, Germany, Spain, Poland, and the UK.

Variables: The questionnaire will be based on the PC. It will contain closed-ended questions (e.g., multiple choice), with no free-text response fields, eliciting responses measuring patient knowledge of the key information in the PC.

Data Sources: Data will be obtained through self-reported web-based questionnaire responses. Before study implementation, the questionnaire will be tested through cognitive pretest interviews with patients in each country. The questionnaire will be cognitively tested in local languages to ensure that the introductory material, consent forms, and questionnaire items (question stems and response choices) are culturally appropriate and are easily and correctly understood by patients similar to those who will participate in the study.

Study Size: The study will target 200 patients with CLL across all countries (approximately 30-50 per country) to allow reasonable precision around estimates of participant knowledge of the safety information regarding TLS.

Data Analysis: The analyses will be descriptive in nature and will include distributions of the responses to all of the individual questions and, if appropriate, summary measures across logical groupings of questions.

Descriptive tables will be generated for the patients overall and stratified by country and other identified variables of interest. Analysis tables will include the frequency and percentage of patients who select each response to each individual question.

Results from this study will be reviewed qualitatively to identify patterns suggesting that the educational activities have been successful (e.g., yielding consistently high percentages of correct responses across

all questions), not successful (e.g., yielding consistently low percentages of correct responses), or partially successful (e.g., yielding high percentages for most responses and low percentages for selected responses). To the extent study sizes allow, the results for each country will be evaluated and interpreted in the context of the local medical practices and the method and timing of the risk-minimisation measures implementation.

Milestones:

Protocol submission to EMA:	Q2 2022
EMA protocol endorsement:	To be determined
Ethical review as required:	Q2 2023
Start of data collection:	Q3 2023
End of data collection:	Q3 2024
Study progress reports:	Annually
Registration in the EU PAS Register:	Prior to start of data collection
Final report of study results:	Q4 2024