# 1 Abstract

**Title:** Cross-sectional Study Evaluating the Effectiveness of Venetoclax Risk-Minimisation Measures Among Haematologists in Europe

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**Keywords:** Venclyxto (venetoclax); post-authorisation safety study; evaluation of risk-minimisation measures; physician survey

**Rationale and background:** Venclyxto (venetoclax), a potent oral inhibitor of B cell lymphoma 2, was initially approved in the European Union (EU), including the United Kingdom (UK), in 2016 as monotherapy in adult patients with chronic lymphocytic leukaemia (CLL) who are unsuitable for or have failed a B cell receptor pathway inhibitor or in adult patients with CLL 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 in 2020, it was approved in combination with obinutuzumab for adult patients with previously untreated CLL (Venclyxto SmPC, 2020).

Tumour lysis syndrome (TLS) has been identified as an important risk in patients who are treated with venetoclax. Tumour lysis syndrome is a known oncology emergency requiring prompt management of metabolic changes to avoid clinical consequences. The risk is higher among patients who have high tumour burden, and patients with renal dysfunction or splenomegaly may be at added risk. These risk factors are not unique to patients taking venetoclax.

Following a validated signal on increased severity of TLS associated with venetoclax in patients with CLL, AbbVie updated the summary of product characteristics (SmPC) in 2021 to provide detailed safety information on TLS and associated risk-minimisation measures. Following review of the updated SmPC by the European Medicines Agency (EMA), a Direct Healthcare Professional Communication (DHPC) was distributed to haematologists in the EU and the UK upon EMA request to communicate the risk of TLS and indicate the importance of strict adherence to dose titration and additional required TLS risk-minimisation measures. Distribution of the DHPC was completed in June 2021.

Additionally, a Patient Card was disseminated to healthcare professionals to be handed out to patients with CLL prior to treatment with Venclyxto to increase patient awareness of the risks of TLS associated with venetoclax. Patient Card distribution was initiated in the EU and UK following the approval of the associated risk-minimisation measures by the national health authorities in each country; therefore, start dates for Patient Card distribution varied by country. While distribution of cards is ongoing, the initial distribution of the Patient Card to healthcare professionals was completed by 30 September 2022.

AbbVie has also implemented a post-authorisation observational study to assess patient knowledge and use of the Patient Card. This study is ongoing under a separate EMA-endorsed study protocol (HMA-EMA Catalogue ID study number 104738).

To meet the required additional pharmacovigilance activities of the venetoclax risk-management plan and evaluate the effectiveness of the revised SmPC and DHPC, this observational post-authorisation safety study aimed to evaluate physician knowledge of the key messages in the revised SmPC and the DHPC for the CLL indication related to the risk of TLS in this population.

**Research question and objectives:** The primary objectives were to assess haematologists' knowledge of the following:

- TLS as a risk of venetoclax treatment for CLL
- Signs/symptoms of TLS
- The importance of strict adherence to venetoclax dose titration and TLS risk-minimisation measures as outlined in the SmPC for all patients, including the following:
  - Assessment of patient-specific factors for the level of TLS risk, including comorbidities, particularly reduced renal function, tumour burden, and splenomegaly before first dose of venetoclax
  - Administration of prophylactic hydration and antihyperuricaemic agents to all patients before first dose of venetoclax
  - Performance of blood chemistry monitoring and tumour burden category assessment
  - Adherence to recommended dose modifications and actions in case of blood chemistry changes or symptoms suggestive of TLS related to venetoclax

The secondary objectives were to ascertain:

- How haematologists receive the DHPC
- The number of participating haematologists who did not receive/do not recall receiving the DHPC
- The receipt and use of the Patient Card

**Study design:** The study was an observational, cross-sectional survey consisting of close-ended questionnaire items to assess physicians' knowledge of the risks of TLS for patients treated with venetoclax for CLL as outlined in the revised SmPC and DHPC for venetoclax. The survey targeted to recruit haematologists who had prescribed venetoclax to at least 1 patient with CLL within the past 4 months (per usual care) from an online panel. Eligible physicians were invited to complete a web-based questionnaire.

**Setting:** The study was conducted in France, Germany, Poland, Spain, and the UK. The selected countries provide adequate geographic representation of European countries and diversity in clinical practice patterns in different settings to maximise the generalisability of the study.

Data collection was initiated in each country approximately 2 years after the distribution of the DHPC and the Patient Card, from 23 November 2023 to 08 January 2024 for Germany, France, Poland, and the UK and to 28 May 2024 in Spain.

**Participants and study size, including dropouts:** From a total of 2,863 physicians invited to participate in the survey, 207 physicians completed the questionnaire and were included in the analysis. Detailed information on the disposition of physicians is described in Section 10.1 (Participants).

**Variables and data sources:** The source of information for the study was self-reported data collected from physicians using a questionnaire with closed-ended response choices. Knowledge-based survey questions included multiple-choice options, often with multiple correct and incorrect answers from which respondents were asked to choose (select all that apply). Yes/no/I don't know response options were also included for certain questions. The questionnaire assessed physician knowledge of the key safety messages regarding TLS outlined in the venetoclax DHPC and revised SmPC and evaluated physicians' receipt and use of the DHPC and Patient Card. Before study implementation, the questionnaire was tested through cognitive interviews with 15 physicians (3 in each country). The interview results were used to optimise language in the questionnaire before fielding the study to maximise the quality of the data collected.

**Results:** Of the 207 physicians who completed the questionnaire, there were 45 in France, 45 in Germany, 25 in Poland, 36 in Spain, and 56 in the UK. The overall survey response rate was 7%. The survey was conducted from November 2023 through May 2024.

*TLS as an important risk factor in treatment of CLL:* Knowledge regarding TLS as an important risk in the treatment of CLL with venetoclax was high. Nearly all physicians were aware that TLS is an important risk (91%) and knew the laboratory definition of TLS (90%); fewer physicians correctly recognised the clinical definition of TLS (73%). Most physicians also knew venetoclax treatment can lead to rapid reduction of tumour volume (83%), the subsequent potential metabolic abnormalities (78%), and that regardless of tumour burden, all patients are at risk for TLS (80%). Knowledge was also high for identifying high tumour burden (86%) and reduced renal function (81%) as factors that increase the risk of TLS, whereas knowledge for splenomegaly was lower (44%).

*Symptoms of TLS:* Physicians' knowledge of the symptoms suggestive of TLS varied. Most physicians recognised "feeling confused" (80%), "irregular heartbeat" (81%), and "fits and seizures" (89%) as possible TLS symptoms, and a lower proportion of

physicians recognised the suggestive symptom "abdominal pain and bloating" (57%). Knowledge of other symptoms suggestive of TLS ranged from 61% to 76%.

*Measures/assessments to perform to assess risk of TLS:* Knowledge was consistently high regarding assessments and prophylactic measures that should be performed prior to initiating venetoclax to reduce the risk of TLS: assessment of tumour burden (92%) and blood chemistry (96%) and administration of antihyperuricaemic agents (87%) and hydration (93%).

*Important safety aspects of the ramp-up/dose-titration schedule:* Knowledge of important safety aspects of dose titration was fairly high, with some exceptions. Most physicians knew that dose titration is required for venetoclax treatment for CLL (91%) and that the titration schedule is designed to decrease the risk of TLS (86%), but fewer physicians correctly indicated that the titration schedule is designed to gradually reduce tumour burden (66%). Almost all physicians (90%) knew that tumour burden and renal function should be considered when determining whether to treat patients in an in-hospital versus outpatient setting. In response to the question on timing of monitoring of blood chemistries and correction of abnormalities, if necessary, for patients taking venetoclax, 27% of physicians selected the response "prior to the first dose of Venclyxto," 34% selected "6 to 8 hours after the first dose of Venclyxto," 20% selected "24 hours after the first dose of Venclyxto," and 17% selected "prior to subsequent doses of Venclyxto." Only 1% of physicians indicated that no blood chemistry monitoring was needed. Relevant information regarding the complexity of this question and physician knowledge is provided in Section 11.3 (Interpretation).

Two-thirds of physicians (63%) correctly indicated that the dose-titration schedule for venetoclax is 5 weeks, with 74% correctly selecting 20 mg as the starting dose and 75% correctly selecting 400 mg as the daily dose. Almost all physicians (86%) knew that strong CYP3A inhibitors are contraindicated during venetoclax initiation and titration. A lower proportion of physicians (39%) knew that reducing the venetoclax dose by 50% was appropriate to manage potential interactions with moderate CYP3A inhibitors, whereas 49% correctly answered that these patients should be monitored for signs of toxicities and adjustment of venetoclax dose may be needed. Only 1% of physicians selected the incorrect response that "no dose adjustment is needed."

*Importance of blood chemistry monitoring and symptom assessment for TLS:* Knowledge of the importance of blood chemistry monitoring and symptoms assessment for TLS varied. Approximately two-thirds of physicians (67%) knew that changes in electrolytes consistent with TLS can occur as early as 6 to 8 hours following the first dose and at dose increases. Most physicians knew that blood chemistry changes (83%) and symptoms suggestive of TLS (82%) may require dose modifications. When asked what to do if blood chemistry or symptoms suggestive of TLS occur, 57% correctly selected withhold the following day's dose and 69% selected resume the dose if resolved within 24-48 hours of the last dose.

*Receipt of DHPC and Patient Card:* Approximately half of all physicians (47%) reported receiving the DHPC, which was distributed in June 2021. The most common means of receipt were email (41%), regular mail (32%), an AbbVie representative (32%), or online (23%). Regardless of whether physicians reported receiving the DHPC, more than half (56%) of physicians reported that they had reviewed the DHPC, and 34% reported that they use it in the management of their patients.

Sixty-one percent of physicians reported receiving Patient Cards, which were distributed in all countries by September 2022. Half of physicians (51%) reported a physician distributed cards to patients, and 39% reported that nurses distributed it. One-quarter of physicians (26%) reported that all patients receive a card, 40% reported that most patients receive it, and 16% reported that half of patients receive it. The main reason for not providing the card to patients was because physicians provide the same information to the patient verbally (52%). Almost all physicians reported that the card is provided to patients either before the start of venetoclax treatment (69%) or at the start of treatment (33%).

*Knowledge stratifications:* There was variation in physicians' knowledge across countries for approximately one-third of the correct responses and general consistency for the remaining correct responses. Overall, knowledge tended to be higher in France, Germany, and Spain and somewhat lower in the UK, with Poland (the country with the fewest surveyed physicians) generally showing the lowest knowledge among all of the countries.

In general, knowledge was higher for physicians who reported they practised in a hospital-based setting (inpatient or outpatient), lower for physicians in general practice, and lowest for private specialty clinics. It is important to note that analysis by practice setting was based on low overall and country-specific numbers of physicians in the general practice and private clinic settings, which preclude making firm interpretations.

**Discussion:** The study met its objectives to evaluate physicians' receipt and use of the DHPC and Patient Card, including knowledge among participating haematologists regarding potential TLS risk associated with venetoclax in the treatment of patients with CLL, TLS assessment and adherence to the TLS risk-minimisation measures following revisions to the SmPC, and dissemination of the DHPC and Patient Card to physicians in select EU countries and the UK.

Although physicians' reported review of the DHPC and distribution of the Patient Card was 56% and 66%, respectively, the relatively high level of knowledge among physicians suggests that the key safety and treatment information is being used by the treating physicians.

Overall, knowledge was high regarding TLS risk associated with venetoclax treatment in patients with CLL, symptoms of TLS, most factors associated with increased risk for TLS, and measures to reduce risk. Knowledge was lower for several items (e.g., splenomegaly

as a risk factor for experiencing TLS, details regarding dosing and monitoring for venetoclax treatment along with moderate CYP3A inhibitor use, withholding dose if patient experiences symptoms suggestive of TLS). Knowledge questions were categorised and then summarised in 6 knowledge areas. Across the 6 categories, knowledge was highest for questions regarding measures/assessments performed to assess TLS risk (median correct responses of 100%) and was lowest for the questions regarding important safety aspects of the ramp-up/dose-titration schedule (median of correct responses of 75%). Overall, of 44 correct responses in the questionnaire, the median percentage of correct responses was 80%, Q1 was 66%, and Q3 was 84%, showing high overall knowledge across all knowledge sections.

In general, the observed patterns of knowledge among the physicians are as expected—with greatest knowledge on the most important risks emphasised in the DHPC and SmPC and lower knowledge on topics that may be less frequently encountered and for which physicians may be more likely to consult the SmPC rather than relying on memory (e.g., details regarding use of venetoclax with CYP3A inhibitors).

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