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# Knowledge, skills, and confidence gaps impacting treatment decision making in relapsed/refractory chronic lymphocytic leukemia and mantle cell lymphoma: a quantitative survey study in France, Germany, and the United States

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## Abstract

**Background** With recent advancements in the treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), healthcare specialists may face challenges making treatment and management decisions based on latest evidence for the optimal care of patients with these conditions. This study aimed to identify specific knowledge, skills, and confidence gaps impacting the treatment of CLL and MCL, to inform future educational activities.

**Methods** Hematologists and hemato-oncologists (HCPs, $n=224$) from France (academic settings), Germany, and the United States (academic and community settings) responded to a 15-minute quantitative needs assessment survey that measured perceived knowledge, skills, and confidence levels regarding different aspects of treatment and management of CLL and MCL patients, as well as clinical case questions. Descriptive statistics (cross tabulations) and Chi-square tests were conducted.

**Results** Four areas of educational need were identified: (1) sub-optimal knowledge of treatment guidelines; (2) sub-optimal knowledge of molecular testing to inform CLL/MCL treatment decisions; (3) sub-optimal skills when making treatment decisions according to patient profile (co-morbidities, molecular testing results); and (4) challenges balancing the risk of toxicities with benefits of treatment. Over one-third of the respondents reported skill gaps when selecting suitable treatment options and prescribing therapies and reported a lack in confidence to initiate and

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manage treatment. Larger gaps in knowledge of guidelines and skills in patient assessment were identified in MCL, compared to CLL.

**Conclusions** This study suggests the need for continuing medical education specifically to improve knowledge of treatment guidelines, and to assist clinicians in developing skills and confidence when faced with clinical decision-making scenarios of patients with specific comorbidities and/or molecular test results, for example, through case-based learning activities.

**Keywords** Chronic lymphocytic leukemia (CLL), Mantle cell lymphoma (MCL), Treatment decisions, Continuing medical education, Continuing professional development, Needs assessment

## Background

Chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) are two relatively rare conditions that although distinct, share some biological, epidemiological, and clinical features [1]. The clinical progression of both hematological malignancies vary, as some tumors are indolent, while others behave aggressively. Understanding the mechanisms underlying disease heterogeneity is increasingly relevant due to the ability to target high risk mutations with novel therapeutics [1]. It is recommended that mutation status of tumor protein p53 (TP53) and the immunoglobulin heavy-chain variable region gene (IGHV) is determined in order to guide treatment of patients with CLL [2] and MCL [3].

The treatment landscape for patients with CLL and MCL has significantly changed with the approval of oral targeted therapies such as B-cell lymphoma 2 (BCL-2) inhibitors, and Bruton's tyrosine kinase (BTK) inhibitors [4–6]. Knowledge of best practices in incorporating and sequencing novel therapies and utilizing risk-adapted treatment approaches are crucial for improved outcomes in the treatment of CLL and MCL [7]. Decisions on the optimal treatment should take into account a patient's prior therapy, remission duration, and preferences. Integrating all of these complex factors when managing relapses can be challenging, especially in the context of time-limited outpatient consultations.

Covalent BTK inhibitors such as ibrutinib have had an important impact on the management of both CLL and MCL with high efficacy and favorable tolerability even in heavily treated patients [8]. BCL2 inhibitors and BTK inhibitors have improved outcomes for patients with CLL, including patients with genetic mutations or unmutated IGHV [9, 10]. While these agents are now standard of care in both CLL and MCL, relapse is inevitable [8, 11]. In addition, the combined use of BTK and BCL2 inhibitors is still investigational [12] and is associated with certain cardiovascular and gastrointestinal toxicities (both CLL and MCL) [13] and with hematological complications (CLL) [14] making long-term usage challenging.

Patients with CLL disease progression after BTK inhibitors and BCL2 inhibitors are generally high-risk patients with poor outcomes, and an approach to monitoring and management should account for their specific clinical needs. New options for this double refractory group now include targeting BTK through a different mechanism, such as with non-covalent BTK inhibitors, utilizing cell therapy such as CD19 Chimeric antigen receptor (CAR) T cells, or allogeneic stem cell transplant which remains an option in certain patient scenarios [8, 15–18].

Though the treatment of MCL has similarly evolved with incorporation of rituximab and high dose cytarabine based induction regimens along with BTK inhibitors, these approaches are associated with short and long-term toxicity [7]. Incorporating targeted therapies, such as BTK inhibitors, into frontline therapy is being investigated as a way to increase response durability, offer more tolerable combination therapy options, and limit use of procedures such as a consolidative autologous stem cell transplant [19, 20]. For patients with relapsed or refractory MCL or CLL, it is recommended that providers discuss advanced treatment options with them, and engage them in treatment decisions as well as care and symptom management for their condition [21].

Treating relapsed/refractory CLL and MCL requires complex decision making and patient input at different stages of treatment. Therefore, patient education about their therapies by providers is crucial. Both oncologists and hematologists play a critical role in making decisions on molecular testing and treatment, and it is essential that they engage and educate patients on the complicated factors associated with their care [13, 22, 23].

The rapidly evolving treatment landscape described above may create challenges for hemato-oncologists and hematologists (HOs/HMs hereafter). To the authors' knowledge, there has been limited research conducted to understand the specific educational needs of the healthcare providers (HCPs) that provide care to patients with relapsing or refractory disease in CLL or MCL. It is important to identify these challenges, to inform future continuing education initiatives aimed to adequately support HOs/HMs. This study aims to identify the education needs of HOs/HMs in the treatment and management of patients with relapsed-refractory CLL or MCL. This study aimed to assess the knowledge, skill, confidence levels, and gaps reported by HOs/HMs in addition to

attitudinal, systemic, and contextual challenges which may interfere with the application of latest knowledge in practice in France, Germany, and United States.

## Methods

### Overall approach

A survey-based, quantitative needs assessment approach [24] was used to identify the educational needs (in the form of current knowledge, skills, and confidence gaps) of HOs/HMs in relation to the treatment and management of patients with relapse-refractory CLL or MCL. The study design and initial tool development were informed by well-established frameworks in the development of evidence-based continuing medical education [25, 26], a review of current literature (including findings from an unpublished qualitative report on clinical challenges in this area), guidelines, and discussions between educational experts (co-authors SP, PL) and clinical experts (co-authors FC, MD, NS). All components of this study were approved by an international independent ethical review board (Veritas IRB, Canada, Tracking Number 2021-2930-9264-1), and all participants agreed to informed consent forms describing the nature and confidentiality of their participation, as well as their rights as a participant. All surveys were completed online.

### Survey design

The data collection tool comprised of an initial screening to ensure eligibility according to the inclusion criteria described above, and a survey. The survey items were grouped into three sections that inquired about CLL only, MCL only, and CLL and MCL together. The first two disease-specific sections included self-report questions to measure respondents' knowledge and skill levels, (using a 5-point Likert-type scale, from 1-none to 5-expert), confidence level (5-point scale, from 1-not at all to 5-very confident), agreement (6-point Likert-like scale, from 1-strongly disagree to 6-strongly agree), and the frequency of specific practices related to CLL or MCL care (5-point scale, from 1-never to 5-always). Survey respondents were presented with disease-specific case scenarios and asked to select the most appropriate option among the nominal response choices presented, and to provide a short justification of their response, to objectively measure knowledge and skills when using molecular tests to guide treatment selection, initiation, and sequencing in relation to current guidelines and best practices. The last section included questions of self-reported confidence, frequency of specific practices and agreements, using the same scales as the first two sections. These questions focused on items unlikely to vary based on the specific disease, such as patient education, management of patient adherence, or perceptions and processes for integration of novel therapies into practice.

The data collection tool was developed in English and translated into French and German so all targeted respondents could participate in their local language. After programming, beta-testing was performed by researchers to verify the quality and functionality of the online survey as intended. The survey was strategically designed to ask relevant questions based on the respondent's expected knowledge and skills. For example, USA respondents were asked about NCCN guidelines [27, 28], while European respondents were asked about European Society for Medical Oncology (ESMO)/European Hematology Association (EHA) [29–31].

### Participants

To be eligible, respondents were required to have: (1) 50% or more of their professional time dedicated to direct patient care (i.e., not solely in research, teaching or in an administrative role); (2) over two years of post-residency experience in hematology or hemato-oncology; (3) a minimum of five CLL and two MCL patients treated in the past year; and (4) prescribed a BTK inhibitor for the treatment of CLL or MCL. In addition, France community settings were not included as these settings were thought by the authors to seldom treat patients with relapsed CLL and MCL. Exclusion was made on the basis of participants not meeting inclusion criteria or quotas for purposive sampling already being full.

Purposive sampling [32] was employed to ensure inclusion of professionals who are most involved in the care of patients with CLL and MCL, and who would therefore be the intended audience of future educational activities that this study seeks to inform. This approach aimed to obtain a balanced distribution of participants across countries and practice settings. Setting was categorized as either academic (including university-affiliated hospitals) or community (private clinics, public non-academic hospitals, solo-practice clinics, community clinics).

### Data collection

Participants were recruited based on their profession and specialty, from a panel of potentially eligible respondents registered to receive invitations for research studies operating in accordance with the guidelines of the ICC/ESOMAR International Code on Market, Opinion and Social Research and Data Analytics [33]. Email invitations included a secure link to a screener to ensure interested respondents met the inclusion criteria. Eligible respondents were provided with a consent form then directed to the online survey.

Data collection occurred between March 16 and April 29, 2022. Participants received compensation according to their country of practice and profession or specialty. As with all study components, compensation was IRB

approved in accordance with international ethical guidelines for equity, transparency, and integrity.

### Analysis

Responses to knowledge and skill items were regrouped into two categories for analysis, out of 5 options: 1=none, 2=basic, or 3=intermediate were labelled "sub-optimal" and 4=advanced, 5=expert were re-coded as "optimal". Responses to the 6-point Likert scale for agreement items were regrouped into four categories: "disagree or strongly disagree," "slightly disagree," "slightly agree", and "agree or strongly agree." The 5-point confidence scale was regrouped as: "sub-optimal" (1=not, 2=slightly, 3=somewhat) and "optimal" (4=confident, 5=very confident). Descriptive statistics such as cross-tabulations were applied for the data analysis using SPSS 27.0 software (IBM Corporation, Armonk, NY, USA). Analysis focused on five sub-groups, based on country and practice setting: France academic, Germany academic, Germany community, USA academic, and USA community. Sub-group analysis by years of practice is also reported, comparing respondents with 2–10, 11–20 and 21 years or more of practice. Findings reported here focus on areas that showed important gaps, with the aim of informing future education.

## Results

### Demographics and clinical characteristics

Results are based on data from 224 eligible survey participants. The median number of patients with CLL and MCL treated by the respondents of the last two years was 90 and 40, respectively. Table 1 details sample demographics and clinical characteristics.

### Main findings

Five key areas of educational needs amongst HOs/HMs were found: (1) knowledge of treatment guidelines; (2) knowledge of molecular testing to inform CLL/MCL treatment decisions; (3) skills when making treatment decisions according to patient profile (comorbidities, molecular testing); (4) challenges balancing the risk of toxicities with benefits of treatment; and (5) challenges related to patient-provider communication and shared decision making. This article will focus on the first four findings, as the fifth one has been described previously [34].

### Knowledge of treatment guidelines

In relation to CLL, higher knowledge gaps about latest guidelines were identified from the community settings in Germany, with 70% reporting sub-optimal knowledge levels of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL). In France, most respondents were knowledgeable of the national guidelines for CLL, however over 34% of participants had a knowledge gap of all other international or European guidelines referenced. In the USA, those in community settings reported sub-optimal knowledge levels of NCCN CLL (36%) guidelines (see Table 2). When respondents were asked what the next steps would be if they suspected CLL disease progression in a case scenario of an older patient progressing on ibrutinib, 21% of respondents selected to start treatment while 79% opted to first order molecular or cytogenic testing. Community-based respondents in Germany (33%) were more likely to start treatment (See Fig. 1). When asked more specifically about their next treatment, 50% selected to start the patient on

**Table 1** Demographics of the respondents by sub-group (based on country and practice setting)

| | France | Germany | | USA | | Total |
|---|---|---|---|---|---|---|
| | Academic | Academic | Community | Academic | Community | |
| | *n*=57 | *n*=22 | *n*=30 | *n*=50 | *n*=65 | *N*=224 |
| ***Distribution of respondents per years of experience*** | | | | | | |
| 2–5 years | 5.3% (3) | 4.5% (1) | 10.0% (3) | 8.0% (4) | 6.2% (4) | 6.7% (15) |
| 6–10 years | 15.8% (9) | 18.2% (4) | 26.7% (8) | 18.0% (9) | 26.2% (17) | 21.0% (47) |
| 11–20 years | 50.9% (29) | 54.5% (12) | 46.7% (14) | 32.0% (16) | 41.5% (27) | 43.8% (98) |
| 21 years or more | 28.1% (16) | 22.7% (5) | 16.7% (5) | 42.0% (21) | 26.2% (17) | 28.6% (64) |
| ***How many patients with mantle cell lymphoma (MCL) have you treated in the past two years?*** | | | | | | |
| Median | 32 | 48 | 40 | 47 | 40 | 40 |
| 25th Percentile | 49 | 68 | 40 | 40 | 38 | 15 |
| 75th Percentile | 150 | 200 | 158 | 423 | 200 | 80 |
| ***How many patients with chronic lymphocytic leukemia (CLL) have you treated in the past two years?*** | | | | | | |
| Median | 95 | 112 | 83 | 95 | 85 | 90 |
| 25th Percentile | 16 | 16 | 10 | 14 | 14 | 43 |
| 75th Percentile | 80 | 69 | 76 | 318 | 85 | 200 |

**Table 2** % (n) reporting no, basic, or intermediate knowledge of guidelines in CLL and MCL per country/practice setting

| Condition | Guideline | France | Germany | | USA | | Total | Chi-Square Sign.* |
|---|---|---|---|---|---|---|---|---|
| | | Academic | Academic | Community | Academic | Community | | |
| CLL | ESMO/EHA | 35% (20) | 29% (6) | 46% (13) | N/A** | N/A** | 37% (39) | $p=0.407$ |
| | iwCLL guidelines | 53% (30) | 59% (13) | 70% (19) | 61% (30) | 50% (31) | 57% (123) | $p=0.402$ |
| | National guidelines | 18% (10) | 20% (4) | 27% (8) | N/A** | N/A** | 21% (32) | $p=0.605$ |
| | NCCN guidelines | N/A** | N/A** | N/A** | 26% (13) | 36% (23) | 32% (36) | $p=0.257$ |
| MCL | ESMO/EHA | 51% (28) | 23% (5) | 69% (20) | N/A** | N/A** | 50% (53) | ***p*=0.005*** |
| | National guidelines | 34% (19) | 10% (2) | 43% (13) | N/A** | N/A** | 32% (34) | ***p*=0.034*** |
| | NCCN guidelines | N/A** | N/A** | N/A** | 33% (16) | 38% (24) | 36% (40) | $p=0.551$ |

* Emboldened values indicate significant differences between country/setting sub-groups at $\alpha \leq 0.05$

** Question not asked to this sub-group of respondents

venetoclax, while 35% selected to start the patient on a second generation BTK inhibitor, such as acalabrutinib.

In relation to MCL, higher knowledge gaps were also identified from the German community settings, with 69% reporting sub-optimal knowledge levels of the EHA ESMO guidelines for MCL. Slightly over half (51%) of participants for France Academic settings reported sub-optimal knowledge levels of these guidelines. Nearly a third of respondents (32%) were sub-optimally knowledgeable of their national guidelines for MCL. In the USA, those in community settings reported sub-optimal knowledge levels of NCCN MCL (38%) guidelines (see Table 2).

No significant differences in years of practice were observed regarding knowledge of the guidelines, or for the case presented above.

#### Molecular tests to inform CLL/MCL decision making

When asked which molecular tests are most important to plan treatment for patients with refractory/relapse CLL, while *del 17p* was selected by 87% of respondents and detection of *TP53* mutation by 84%, only 57% reported IGHV as important. The molecular test that was the least frequently selected by respondents as important to plan treatment for CLL was presence of Phospholipase C Gamma 2 (*PLCG2)* mutation (21%) (see Table 3).

When asked the same question to plan treatment for patients with refractory/relapse MCL, *del 17p* was also the most often selected by 74% of respondents, followed by detection of *TP53* mutation (73%). The molecular test that was the least frequently selected was again presence of *PLCG2* mutation (19%) (see Table 3).

Knowledge of the impact of molecular test results on CLL treatment planning was reported at sub-optimal levels for a *PLCG2* mutation (66% of respondents). This was followed by *BTK* mutation (39%), with a significant difference between years of practice (2–10 years 52%, 11–20 years 60%, 21+years 74%, $p=0.032$). Other knowledge gaps were reported, in a lesser proportion, for the *del 17p* (30%; 2–10 years 41%, 11–20 years 30%, 21+years 20%, $p=0.048$) and *TP53* mutations (31%; 2–10 years 45%, 11–20 years 31%, 21+years 18%, $p=0.005$). Table 3 provides details per country and practice setting.

When considering treatment planning for MCL, knowledge was reported at sub-optimal levels for a *PLCG2* mutation (59% of respondents). This was followed by *IGHV* mutation status for MCL (sub-optimal knowledge 54% compared to CLL: 7%) and *BTK* mutation (48%; 2–10 years 65%, 11–20 years 44%, 21+years 39%, $p=0.008$). Other knowledge gaps were reported, in a lesser proportion, for the *del 17p* mutation (43%; 2–10 years 62%, 11–20 years 37%, 21+years 33%, $p=0.001$) and the *TP53* mutation (41%; 2–10 years 59%, 11–20 years 34%, 21+years 33%, $p=0.003$), except in community settings in Germany, where the gaps remained high for both mutations (del 17p: 56%) and (TP53: 59%) (see Table 3).

#### Skills when making treatment decisions according to patient profile (comorbidities, molecular testing)

In relation to CLL, over a quarter of participants (27%; 2–10 years 39%, 11–20 years 27%, 21+years 17%, $p=0.025$) reported their skills at sub-optimal levels when assessing which patients needed molecular tests. Nearly one third reported sub-optimal skill levels making treatment decisions based on those tests (32%; 2–10 years 48%, 11–20 years 29%, 21+years 22%, $p=0.005$; see Table 4). 35% of respondents reported skill gaps in treatment decision making with patients with CLL who have many comorbidities (Germany, community, 40%; USA

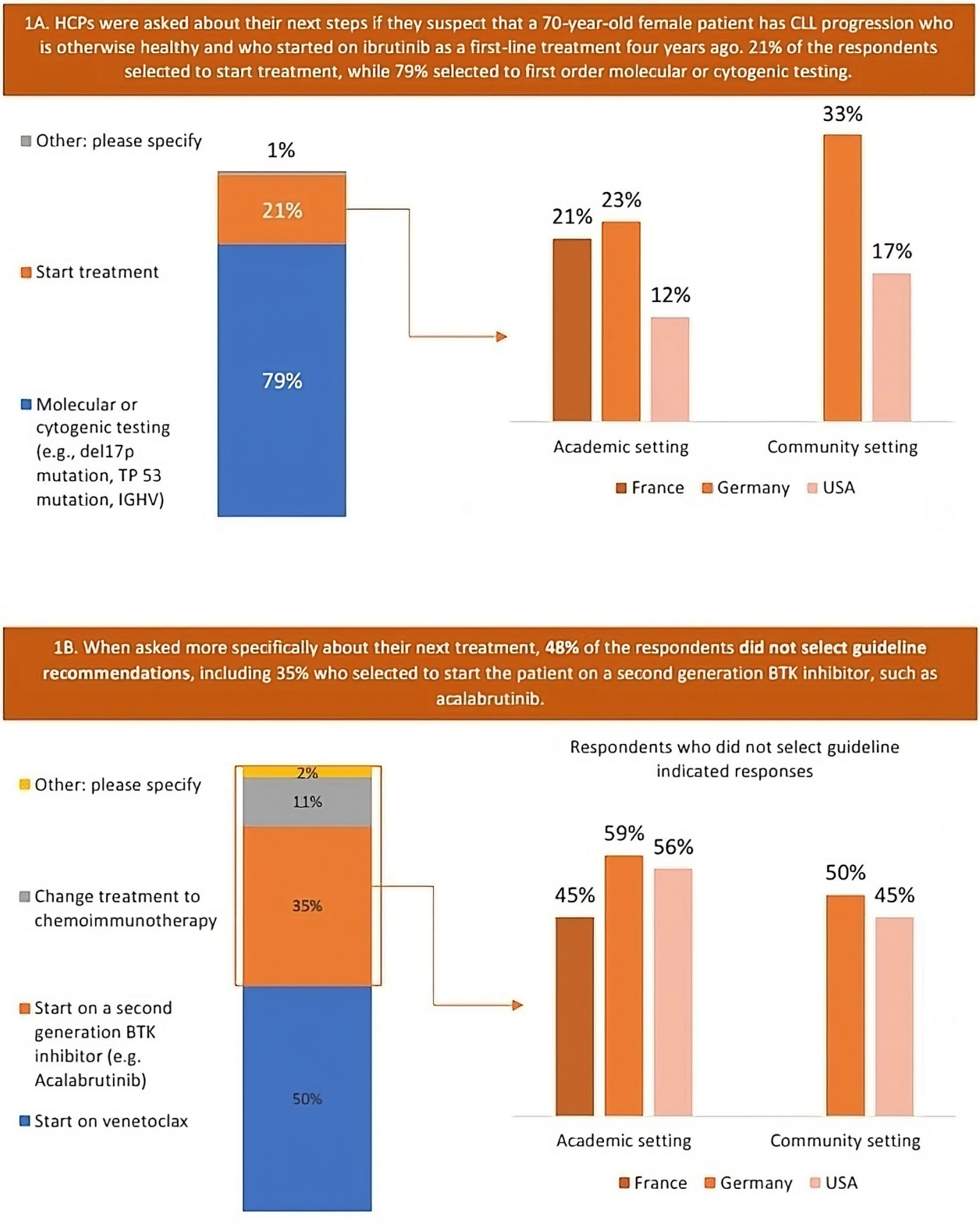


**Fig. 1** Response to a CLL case scenario

**Table 3** % reporting sub-optimal knowledge* of the impact of molecular test results on treatment planning for each mutation and % who perceived test as "important" for planning treatment for refractory/relapse CLL/MCL by country and practice setting

| Condition | Mutation | France | Germany | | USA | | Total | Chi-Square Sign.* |
|---|---|---|---|---|---|---|---|---|
| | | Academic | Academic | Community | Academic | Community | | |
| ***% who report sub-optimal knowledge** test results' impact on treatment planning*** | | | | | | | | |
| **CLL** | **Del 17p** | 26% (15) | 19% (4) | 30% (9) | 35% (17) | 34% (22) | 30% (67) | $p=0.614$ |
| | **TP53 mutation** | 27% (15) | 24% (5) | 27% (8) | 33% (16) | 39% (24) | 31% (68) | $p=0.577$ |
| | **IGHV mutational status** | 25% (14) | 33% (7) | 43% (13) | 40% (19) | 42% (27) | 37% (80) | $p=0.289$ |
| | **BTK mutation** | 34% (19) | 41% (9) | 59% (17) | 37% (18) | 34% (22) | 39% (85) | $p=0.187$ |
| | **PLCG2 mutation** | 64% (36) | 73% (16) | 71% (20) | 77% (37) | 55% (35) | 66% (144) | $p=0.127$ |
| **MCL** | **Del 17p** | 43% (24) | 27% (6) | 56% (15) | 42% (21) | 44% (28) | 43% (94) | $p=0.407$ |
| | **TP53 mutation** | 36% (20) | 36% (8) | 59% (16) | 44% (22) | 37% (23) | 41% (89) | $p=0.260$ |
| | **IGHV mutational status** | 57% (32) | 41% (9) | 73% (19) | 55% (26) | 48% (29) | 54% (115) | $p=0.158$ |
| | **BTK mutation** | 52% (29) | 38% (8) | 71% (20) | 42% (21) | 44% (28) | 48% (106) | $p=0.076$ |
| | **PLCG2 mutation** | 71% (40) | 75% (15) | 71% (20) | 71% (35) | 59% (37) | 59% (147) | $p=0.454$ |
| ***% Who selected test as "important" to plan treatment for patients with refractory/relapse CLL/MCL*** | | | | | | | | |
| **CLL** | **Del 17p** | 89% (6) | 91% (2) | 83% (5) | 92% (4) | 80% (13) | 87% (30) | $p=0.316$ |
| | **TP53** | 86% (8) | 86% (3) | 77% (7) | 88% (6) | 82% (12) | 84% (36) | $p=0.674$ |
| | **IGHV** | 51% (28) | 59% (9) | 60% (12) | 58% (21) | 60% (26) | 57% (96) | $p=0.865$ |
| | **BTK** | 42% (33) | 50% (11) | 33% (20) | 48% (26) | 62% (25) | 49% (115) | $p=0.087$ |
| | **PLCG2** | 21% (45) | 14% (19) | 13% (26) | 12% (44) | 34% (43) | 21% (177) | ***p*=0.030*** |
| **MCL** | **Del 17p** | 75% (14) | 73% (6) | 57% (13) | 76% (12) | 80% (13) | 74% (58) | $p=0.192$ |
| | **TP53** | 70% (17) | 77% (5) | 53% (14) | 80% (10) | 77% (15) | 73% (61) | $p=0.091$ |
| | **IGHV** | 25% (43) | 27% (16) | 30% (21) | 52% (24) | 52% (31) | 40% (135) | ***p*=0.004*** |
| | **BTK** | 35% (37) | 50% (11) | 37% (19) | 48% (26) | 58% (27) | 46% (120) | $p=0.090$ |
| | **PLCG2** | 14% (49) | 23% (17) | 13% (26) | 14% (43) | 28% (47) | 19% (182) | $p=0.215$ |

* Emboldened values indicate significant differences between country/setting sub-groups at $\alpha \leq 0.05$.

**Sub-optimal = % of respondents reporting no, basic, or intermediate knowledge

academic, 30%, community, 32%; see Table 4) (2–10 years 45%, 11–20 years 26%, 21+years 22%, $p=0.008$).

In relation to MCL, over a third of participants reported their skills at sub-optimal levels when assessing which patients needed molecular tests (34%) or when making treatment decisions based on those tests (37%; see Table 4). No significant difference between experience sub-groups were observed.

Regarding sequencing second line therapy for CLL, fewer skill gaps were reported in the academic setting of Germany (14%, vs. 34% in total sample, Table 5), and in more experienced participants (2–10 years 49%, 11–20 years 32%, 21+years 22%, $p=0.006$). However, 40% of all respondents reported sub-optimal skill levels when selecting next line of treatment for CLL after discontinuing BCL-2 inhibitors (2–10 years 54%, 11–20 years 35%, 21+years 33%, $p=0.025$). Respondents reported skill gaps

**Table 4** % (n) who report sub-optimal* skills when planning or selecting treatment

| Condition | Skill Item | France | Germany | | USA | | Total | Chi-Square Sign.** |
|---|---|---|---|---|---|---|---|---|
| | | Academic | Academic | Community | Academic | Community | | |
| **CLL** | Assessing which patients need a molecular test or genetic test | 35% (20) | 9% (2) | 27% (8) | 24% (12) | 29% (19) | 27% (61) | $p=0.212$ |
| | Making treatment decisions based on molecular tests | 32% (18) | 23% (5) | 33% (10) | 28% (14) | 40% (25) | 32% (72) | $p=0.569$ |
| | Incorporating recommendations from guidelines to adjust treatment*** | 32% (18) | 27% (6) | 40% (12) | 36% (18) | 37% (24) | 35% (78) | $p=0.857$ |
| | Treatment decision making with patients who have many comorbidities*** | 28% (16) | 14% (3) | 40% (12) | 30% (15) | 32% (21) | 30% (67) | $p=0.342$ |
| **MCL** | Assessing which patients need a molecular test or genetic test | 42% (24) | 14% (3) | 41% (12) | 31% (15) | 34% (22) | 34% (76) | $p=0.156$ |
| | Making treatment decisions based on molecular tests | 42% (24) | 23% (5) | 41% (11) | 29% (14) | 42% (26) | 37% (80) | $p=0.301$ |

*Sub-optimal = % of respondents reporting no, basic, or intermediate skills

** Bolded values indicate significant differences between country/setting sub-groups at $\alpha \leq 0.05$.

*** Not asked for MCL

when selecting next line of treatment after discontinuing BTK inhibitors (33%), with elevated levels in in Germany's community setting (40%, in contrast to the academic settings in the USA where only 29% reported a skill gap in this area; Table 5) and differences between experience sub-groups (2–10 years 46%, 11–20 years 30%, 21+years 27%, $p=0.043$). This.

Similar skill gaps were reported when considering MCL, with lower frequency of sub-optimal levels in the academic setting of Germany for sequencing second line therapy (23%, vs. 32 for overall sample; Table 5). Differences by experience sub-group were observed (2–10 years 45%, 11–20 years 31%, 21+years 20%, $p=0.012$). Respondents reported skill gaps when selecting next line of treatment for MCL after discontinuing BTK inhibitors (39%; no significant difference by experience), with higher levels in in Germany's community setting (53%) followed by the academic setting in France (47%).

A skill gap in sequencing treatment in patients on anti-coagulation medication with a bleeding disorder, or with cardiac risk factors was found amongst over a third of respondents (both CLL and MCL) mainly in the academic setting of France (42%). The respondents in academic settings in Germany (18%) reported a relatively low level of skill gaps when sequencing treatment in patients with such conditions. No difference by experience was observed.

### Challenges balancing the risk of toxicities with benefits of treatment

When considering CLL, 42% of participants slightly agreed that "certain BTK inhibitors have a reduced risk for cardiac toxicity" (Fig. 2), while another 42% agreed or strongly agreed. Elevated percentages of strong to light disagreement were observed in Germany's community setting (20%) and France's academic setting (21%), while more experienced participants agreed or strongly agreed with the statement in a higher proportion (2–10 years 35%, 11–20 years 38%, 21+years 53%, $p=0.026$).

When considering MCL, similarly, the majority of respondents (76%) strongly to slightly agreed with that statement, with elevated numbers of disagreement in Germany's community setting (27%) (Fig. 2), and more experienced participants more frequently agreed or strongly agreed with the statement (2–10 years 26%, 11–20 years 35%, 21+years 45%, $p=0.038$).

Back to CLL, the responses from more than one-third (34%) of respondents showed skill gaps weighing risks and benefits of using BTK inhibitors according to CLL patient profile (Table 5). This gap was more pronounced in less experienced respondents (2–10 years 51%, 11–20 years 29%, 21+years 27%, $p=0.006$). In the USA academic setting, 32% reported low confidence when selecting treatment for patients with relapsed/refractory CLL in consideration of potential side effects and toxicities (Table 6). When initiating treatment of CLL with acalabrutinib after discontinuing ibrutinib treatment due to intolerance or toxicity, suboptimal confidence level was found among 33% of respondents. No difference by experience was observed for these two confidence gaps.

When considering MCL, 26% of respondents reported low confidence when selecting treatment for patients with relapsed/refractory MCL in consideration of potential side effects and toxicities (Table 6; no difference by experience), with elevated sub-optimal levels in the USA academic setting, where 32% reported low confidence.

When asked to consider both CLL and MCL, 30% of respondents had a confidence gap avoiding cumulative toxicities when initiating treatment with new agents, and lower confidence levels were reported when selecting treatment in consideration of potential side effects and

**Table 5** % reporting sub-optimal* skills selecting, monitoring and managing, and sequencing treatment

| Skill item | | France | Germany | | USA | | total | Chi-Square Sign.** |
|---|---|---|---|---|---|---|---|---|
| | | Academic | Academic | Community | Academic | Community | | |
| For CLL | | | | | | | | |
| Weighing risk and benefit of treatment using BTK inhibitors according to patient profile | | 41% (23) | 27% (6) | 30% (9) | 33% (16) | 34% (22) | 34% (76) | $p=0.471$ |
| Monitoring and managing side effects from… | BTK inhibitors | 40% (23) | 23% (5) | 33% (10) | 29% (14) | 38% (25) | 35% (77) | $p=0.513$ |
| | BCL-2 inhibitors | 34% (21) | 27% (6) | 43% (13) | 29% (14) | 37% (23) | 35% (77) | $p=0.639$ |
| Sequencing treatment … | … in patients on anti-coagulation or with bleeding disorders | 44% (25) | 27% (6) | 37% (11) | 37% (18) | 41% (26) | 39% (86) | $p=0.721$ |
| | … in patients who have cardiac risk factors | 39% (22) | 14% (3) | 30% (9) | 316% (15) | 39% (25) | 33% (74) | $p=0.214$ |
| | … for 2nd line therapy | 42% (24) | 14% (3) | 40% (12) | 27% (13) | 36% (23) | 34% (75) | $p=0.141$ |
| | … for selecting next line of treatment after discontinuing BTK inhibitors | 33% (19) | 27% (6) | 40% (12) | 29% (14) | 35% (23) | 33% (74) | $p=0.811$ |
| | … for Selecting next line of treatment after discontinuing BCL-2 inhibitors*** | 42% (24) | 36% (8) | 53% (16) | 35% (17) | 36% (23) | 40% (88) | $p=0.484$ |
| ***For MCL*** | | | | | | | | |
| Monitoring and managing side effects from… | CAR-T cell therapy | 53% (30) | 52% (11) | 72% (21) | 40% (19) | 44% (28) | 50% (109) | $p=0.074$ |
| Sequencing treatment … | … in patients on anti-coagulation or with bleeding disorders | 46% (26) | 18% (4) | 43% (13) | 31% (15) | 42% (27) | 39% (85) | $p=0.148$ |
| | … in patients who have cardiac risk factors | 42% (24) | 18% (4) | 47% (14) | 33% (16) | 36% (22) | 36% (80) | $p=0.237$ |
| | … for 2nd line therapy | 37% (21) | 23% (5) | 50% (15) | 25% (12) | 27% (17) | 32% (70) | $p=0.094$ |
| | … for selecting next line of treatment after discontinuing BTK inhibitors | 47% (27) | 32% (7) | 53% (16) | 29% (14) | 33% (21) | 38% (85) | $p=0.102$ |

*Sub-optimal = % of respondents reporting no, basic, or intermediate knowledge

** Emboldened values indicate significant differences between country/setting sub-groups at $\alpha \leq 0.05$

*** Not asked for MCL

toxicities for MCL compared to CLL. (see Table 6; no difference by experience).

## Discussion

This study assessed the current educational needs for HCPs involved in CLL and/or MCL, identifying specific knowledge, skills, and confidence gaps in the treatment of patients with relapsed/refractory CLL or MCL. The findings indicate a need to improve, in both disease conditions, use of current guidelines, knowledge of molecular tests to guide treatment decisions, and the skills to select the right treatment according to the patient profile of comorbidities and molecular test results. In addition, efforts should be made to increase HCP's confidence when faced with complex patient needs.

Knowledge of guidelines was lower in community settings, especially when treating MCL, which is not surprising given the rarity of this disease, even compared to CLL, and complex cases are typically referred to academic centers. Certain gaps were anticipated due to regional variation in access, setting and standard of care [35], however the lack of familiarity with current standards of care may limit possible treatment options offered to patients, prioritizing agents HCPs are most familiar with, which can contribute to inconsistencies in patient care depending on the treating HCP [36]. The fact that over a third of HCPs would sequence acalabrutinib after progression on ibrutinib (see second question of case scenario) is not aligned with the recommendations of guidelines [27, 30, 31], and demonstrate an important need for education.

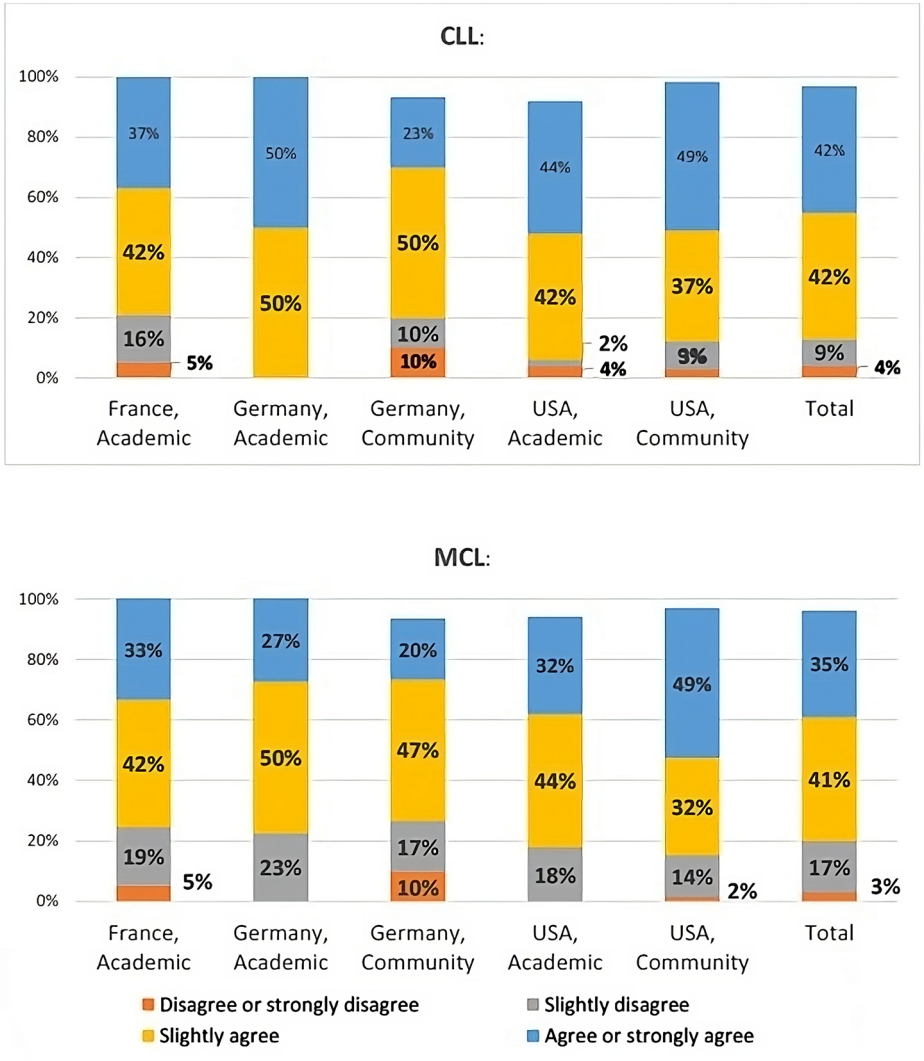


**Fig. 2** % Agree / Disagree: "Certain BTK inhibitors have reduced risk for cardiac toxicity"

**Table 6** % who report sub-optimal* confidence when selecting and initiating treatment

| Condition | Confidence item | France | Germany | | USA | | total | Chi-Square Sign.** |
|---|---|---|---|---|---|---|---|---|
| | | Academic | Academic | Community | Academic | Community | | |
| **CLL** | Selecting treatment in consideration of potential side effects and toxicities | 12% (7) | 18% (4) | 13% (4) | 32% (16) | 17% (11) | 19% (42) | $p=0.092$ |
| | Initiating treatment with acalabrutinib after discontinuing ibrutinib treatment due to intolerance or toxicity*** | 35% (20) | 27% (6) | 50% (15) | 22% (11) | 34% (22) | 33% (74) | $p=0.145$ |
| **MCL** | Selecting treatment in consideration of potential side effects and toxicities | 23% (13) | 18% (4) | 27% (8) | 32% (16) | 27% (17) | 26% (58) | $p=0.744$ |
| **CLL & MCL** | Avoiding cumulative toxicities when initiating treatment with new agents | 39% (22) | 27% (6) | 20% (6) | 31% (15) | 28% (18) | 30% (67) | $p=0.459$ |

*% respondents who reported not, slightly, or somewhat confident

** Emboldened values indicate significant differences between country/setting sub-groups at $\alpha \leq 0.05$

*** This item was not asked for MCL

BTK mutation testing is relatively new, particularly in Europe, which may necessitate education to enhance understanding on when it may be appropriate [19]. The clinical utility of PLCG2 is currently limited [37] but considering practice trends, it may have increased utility in the future [38]. In anticipation of emerging needs, early continuing education for oncologists and hematologists should be planned and developed. Furthermore, this study confirms that del p17, TP53, and IGHV are currently the most frequently used tests for treatment decision making [39]. However, it remains surprising that even these tests were not ordered with greater fidelity, especially with IGHV which was only deemed to be important by 57% of providers. This might be attributed to the shifting treatment landscape. IGHV mutation status, while providing useful prognostic information, is only essential when considering chemoimmunotherapy as a treatment option and in recent years, more targeted approaches have surpassed chemoimmunotherapy among the preferred treatment options [40]. This suggests that educational efforts should seek to focus on improving knowledge of these molecular tests.

This study observed that when a given molecular test was perceived as less relevant in treatment decision making, the HCP's level of knowledge of it was low. Increasing awareness of current and potential relevance of a test may encourage HCPs to improve their knowledge and familiarity broadening their repertoire of valuable treatment options to address the observed challenges in treatment selection, especially in complex cases. Similarly, access to different molecules in the treatment of patients with CLL or MCL (e.g., BTK inhibitors, BCL2 inhibitors) may have influenced the level of importance at which they were perceived, which in turn would influence the HCP's reported levels of knowledge and skills. Even when molecules were approved around the same time in the three countries, official reimbursement processes may differ, which ultimately impact access.

Shanbhag (2021) [41] has described concerns about the side effects of therapeutic advancements in the treatment landscape of CLL. Although such advancements have improved treatment tolerability, they have not completely mitigated the risk of cardiac toxicity. This study found skill gaps when selecting treatment that avoids those risks posed by potential toxicities. Likewise, skill gaps were also identified regarding HCPs' selection of treatment for patients with cardiac risk factors and other comorbidities, or those with a full treatment history and a need for novel therapies. This suggests management of patients with complex profiles should be a priority of future educational efforts, based on emerging evidence for best practices. Recent studies have shown that interactive problem-based continuing medical education (CME) using case studies [42], and online certified CME activities [43] relevant to the HCP's practice needs, can improve skills.

As we found relatively smaller gaps when HCPs are based in academic settings, a greater focus should be placed on offering education on this topic for those in community settings, especially for HCPs treating more patients with relapsed MCL. This study pointed to country and setting variations that should be considered when designing relevant educational initiatives, but some more local differences may exist. For example, though our results show that overall, German HCPs in academic settings show less need for continuing education on selecting 2nd line treatments, there could be value in a closer examination to quantify needs in specific settings, to inform local initiatives. Pre-test evaluations prior to education sessions may help focus the conversation on areas of deficiencies, rather than a one-size fits all approach to instruction.

In both CLL and MCL, for most of the items that showed a difference in years of practice, the gaps were higher among respondents with the least amount of experience. To be the most effective, medical education solutions should target community oncologists early in their practice, while still including more experienced practitioners, given that in most cases, the percentage of these experienced practitioners having knowledge or skill gaps was still sufficiently high enough to warrant medical education.

Our findings suggest that future education should build core knowledge and appreciation of the established clinical relevance of molecular tests, support standard algorithms for clinical management with a goal to improve provider confidence in the management of complex malignancies like CLL and MCL. This could involve peer-guided hands-on training, combined with more traditional knowledge building efforts in the form of lectures and journal clubs within the hematology and oncology departments.

### Limitations

Most survey items asked participants to self-assess their current knowledge and competencies according to what is expected of them in their professional role, and hence reflects individual perceptions, rather than objective and validated assessments by a third-party evaluator. Thorough and objective knowledge and competency-based assessments may be possible in the scope of an in-depth course lasting multiple weeks, but is highly difficult to achieve in the scope of a research-based needs assessment, that utilizes reasonable methods (i.e., 15-minute online survey) to attract sufficient interest. To address this limitation, a few case studies were included in the survey to gather a more objective assessment of respondents' clinical decision-making and applied knowledge

of best practices. In addition, the quantitative nature of the study limits the nuances in responses that would best reflect the actual knowledge, judgment, or belief of a respondent. These issues were mitigated in part by the inclusion of open answer options for some, though not all items, to ensure the survey length is within its stated duration. While the survey was critically reviewed by both educational and clinical experts collaborating on this project to verify full and consistent comprehension of survey questions and items, the divergence in individual interpretation of survey questions by the respondents themselves was not assessed. The validity of few findings could be questioned, as was the case for the reported caseload of MCL and CLL patients; numbers were higher than expected, which suggests that facility, rather than individual, numbers were reported (see Table 1, range and median values). This did not impact the conclusions of the study, as patient caseload was not a core variable in the final analysis. However, as in any evidence-base generation, validation of findings could be strengthened by other research groups conducting similar initiatives using complementary methods (e.g., interviews, third-party observations). Unfortunately, to co-authors knowledge, these types of studies are currently missing on the topic of educational needs for HCPs treating MCL and/or CLL. Sample size by country was small and may not be a comprehensive representation of the experience of all HCPs who treat CLL and MCL in each country. Data should be interpreted as an identification of trends, which can provide relevant indicators for educators planning and developing continuing education activities [25, 26], but should not replace local validation of the challenges when appropriate.

### Implications

The findings of this study have implications for clinical practice and CME, continuing professional development, and performance improvement / quality improvement initiatives for CLL and/or MCL treatment decision making. The results can be applied in the design of curriculum for HCP workplace training, for example in the management of cardiac toxicity with covalent BTK inhibitors [35, 36]. Novel educational approaches for HOs/HMs have shown significant impact on knowledge, competence and confidence – a recent interactive CME program in CLL used educational videos and in-person facilitation along with assessment with positive results [43]. Our study and others suggest that incorporating educational initiatives in a real-world setting (clinical practice) can demonstrate the relevance and broad impact of addressing practice gaps, while maximizing the capacity of the setting and the care they provide.

Overall, there is a need for additional research to better understand the factors explaining gaps observed in this study. Further empirical research on the effectiveness and factors that support utilization of CLL and MCL guidelines in practice would be necessary. Research to understand barriers that HCPs face when trying to engage patients in treatment planning and when adopting the latest tests or practices for CLL and/or MCL would enrich these efforts. Similarly, qualitative research could also complement and add depth and insight into any of the issues mentioned.

## Conclusions

As new treatments emerge, and overall survival increases, HCPs in this field will have access to a broadening arsenal of treatment to choose from. Continuing professional development programs must stay current with the educational needs resulting from these scientific and clinical advancements and consistently aim to support HCPs in acquiring and further developing relevant knowledge, skills and confidence. Findings from this study can be leveraged by curriculum developers and education providers to develop tailored educational programs that meet the needs of oncology professionals caring for patients with relapsed or refractory CLL or MCL.

#### Abbreviations

| | |
|---|---|
| CLL | chronic lymphocytic leukemia |
| MCL | mantle cell lymphoma |
| TP53 | tumor protein p53 |
| IGHV | Immunoglobulin heavy-chain variable region gene |
| BCL-2 | B-cell lymphoma 2 |
| BTK | Bruton's tyrosine kinase |
| CAR | chimeric antigen receptor |
| NCCN | National Comprehensive Cancer Network |
| EHA | European Hematology Association |
| ESMO | European Society for Medical Oncology |
| iwCLL | the International Workshop on Chronic Lymphocytic Leukemia |
| Hos/HMs | hemato-oncologists/hematologists |
| HCPs | Healthcare Providers |
| IRB | Independent review board |
| PLCG2 | Phospholipase C Gamma 2 |
| CME | Continuing Medical Education |

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#### Author contributions

SP, SM, and RDF contributed to project conceptualization and funding acquisition. SP, PL, and SM designed the study. PL led the development of data collection tools, monitoring of data collection, and analysis of quantitative data. FC, MD, and NS formed a steering committee of clinical subject matter experts who contributed to the refinement of the study design and tools. All authors contributed to the interpretation of the findings. SP and PL directly supervised development of the original draft of the manuscript, which was critically reviewed by FC, MD, NS, RDF, CEM, and SM for important intellectual content. All authors have approved of the final version of the manuscript and have agreed to be accountable for all aspects of the work.

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**Data availability**
Aggregated and anonymized data used and/or analysed in the current study will be made available to the editors of the journal for review or query upon reasonable request to the corresponding author.

## Declarations

**Ethics approval and consent to participate**
All components of this study were approved by an international independent ethical review board (Veritas IRB, Canada, Tracking Number 2021-2930-9264-1), and all participants agreed to informed consent forms describing the nature and confidentiality of their participation, as well as their rights as a participant.

**Consent for publication**
Not applicable.

**Competing interests**
SP and PL are employees of AXDEV Group Inc. SM is CEO & founder of AXDEV Group Inc., AXDEV Global Inc., and AXDEV Europe GmbH. NS reports participation on advisory boards and/or consultancy for Kite Pharma, BMS-Juno, TG therapeutics, Miltenyi Biotec, Lilly-LOXO, Epizyme, Incyte, Novartis, Janssen, Seattle Genetics, and Umoja; and research funding and honoraria from Miltenyi Biotec.FC reports participation on advisory boards and/or consultancy for AbbVie, Lilly, Janssen, Astra Zeneca.MD reports participation on advisory boards for Astra Zeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, Roche. He has research funding from Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche, and honoraria from Astra Zeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis, Roche. MD is an associate editor for HemaSphere. NS, FC, and MD received research honoraria from AXDEV Global for their contribution to the study design, review of research tools, and interpretation of the findings from this study. RDF and CEM are employees of Eli Lilly and Company.

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## Publisher's Note