Review Article

Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France

Loïc Ysebaert,[1] Stéphane Ederhy,[2] Véronique Leblond,[3] Stéphanie Malartre,[4] Anaïs Portalier,[3] Vincent Sibaud,[5] Cécile Tomowiak,[6] Jérémie Zerbit[7], on behalf of the Delphi Acalabrutinib Safety Study Group*

Abstract

Acalabrutinib, a second-generation Bruton's tyrosine kinase inhibitor (BTKi), offers an improved safety profile compared to first-generation inhibitors like ibrutinib. While BTKi guidelines exist, practical differences between BTKis—such as drug interactions and tolerance—are not fully addressed. Therefore, a consensus on acalabrutinib use would benefit the medical community. This 2-round Delphi study involved hematologists, pharmacists, cardiologists, dermatologists, and nurse practitioners throughout France to establish consensus-based practical guidance on managing adverse events (AEs) associated with acalabrutinib in chronic lymphocytic leukemia. Key findings highlighted the need for a hospital pharmacist to analyze drug interactions before starting acalabrutinib. Additionally, the experts' opinion was to avoid the concomitant use of acalabrutinib with strong CYP3A inhibitors due to an increased risk of toxicity and with strong CYP3A inducers due to potential efficacy concerns. Importantly, our study did not find contraindications for acalabrutinib in patients with current or previous atrial fibrillation. The panel emphasized the importance of measuring blood pressure at every clinical visit for patients treated with acalabrutinib and opposed the initiation of acalabrutinib in patients on both aspirin and clopidogrel. For invasive dermatological or dental procedures, acalabrutinib should be discontinued 4 days prior and resumed 48 hours postprocedure in the absence of bleeding. Additionally, patients should be informed about the risk of headaches, particularly during the first month of treatment, and paracetamol use in combination with caffeine is recommended for managing grade $\geq$ 2 headaches under acalabrutinib treatment. This Delphi study underscored the effectiveness of a collaborative process in enhancing the management of acalabrutinib-associated AEs.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 000, No.xxx, 1–9

Keywords: Acalabrutinib, Adverse events, DELPHI, Consensus, Clinical management

Introduction

Chronic lymphocytic leukemia (CLL) is a clonal mature B-cell neoplasm characterized by an excessive number of lymphocytes. It is one of the most common adult leukemias in Western countries.[1,2] In France, more than 4,600 new cases of CLL are diagnosed each year, with a median age of diagnosis at 71 years for men and 73 years for women.[3] The treatment of CLL has shifted significantly in recent years from chemoimmunotherapy to oral targeted therapies, which includes Bruton's tyrosine kinase inhibitors (BTKis) such as ibrutinib (the first-in-class covalent inhibitor approved in 2014), and other second-generation covalent (tirabrutinib, acalabrutinib, zanubrutinib) or noncovalent (pirtobrutinib) inhibitors.[4,5] BTK,

[1]Department of Hematology, Cancer University Institute of Toulouse Oncopole, Toulouse, France
[2]Department of Cardiology, Saint-Antoine Hospital, Paris, France
[3]Department of Hematology, Sorbonne University, Pitié-Salpêtrière Charles Foix University Hospitals, Paris, France
[4]Department of Hematology, Centre Léon Bérard, Lyon, France
[5]Department of Oncodermatology, Cancer University Institute of Toulouse Oncopole, Toulouse, France
[6]Department of Hematology and Cellular Therapy, Poitiers University Hospital, Poitiers, France
[7]Department of Pharmacy, Paris Public Hospital at Home (HAD AP-HP), University Hospitals of Paris, Paris, France

Submitted: Oct 2, 2024; Accepted: Oct 20, 2024; Epub: xxx

Address for correspondence: Loïc Ysebaert, MD PhD, Department of Hematology, Cancer University Institute of Toulouse Oncopole, 1 Avenue Irène Joliot-Curie, 31059, Toulouse, France
E-mail contact: ysebaert.loic@iuct-oncopole.fr

* **The Delphi Acalabrutinib Safety Study Group** participants who contributed to the 2 Delphi rounds (listed in alphabetical order) are: *Hematologists:* Omar Benbrahim, Orléans; Lucile Bussot, Grenoble; Julien Colle, Marseille; Caroline Dartigeas, Tours; Sophie de Guibert, Rennes; Jean-Luc Delassus, Meaux; Jehan Dupuis, Paris; Abderrazak El Yamani, Blois; Cyril Faure, Vesoul; Pierre Feugier, Nancy; Luc-Matthieu Fornecker, Strasbourg; Stéphane Lepretre, Rouen; Vincent Levy, Bobigny; Morgane Nudel, Lille; Damien Roos-Weil, Paris; Laurence Simon, Corbeil-Essonnes; Nicolas Stocker, Paris; Emmanuelle Tchernonog, Montpellier; Lise Willems, Paris. *Advanced practice nurses:* Sandrine Buray, Rouen; Gisèle Compaci, Toulouse; Marie-Caroline Mayeux, Nancy. *Pharmacists:* Clément Carbasse, Nîmes; Claire Davoine, Bobigny; Jean-François Huon, Nantes; Marie Kroemer, Besançon.

2152-2650/$ - see front matter
https://doi.org/10.1016/j.clml.2024.10.013

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

a docking protein with kinase activity, plays a crucial role in the downstream activation of the B-cell antigen receptor (BCR) and other cell surface receptors, which are fundamental in regulating CLL cell proliferation, migration, and survival.[4] However, BTK and its upstream regulators are also present in normal cells of the immune and vascular systems, heart, and platelets. This widespread distribution accounts for both on-target therapeutic effects and off-target side effects typical of BTKis.[6]

Nevertheless, among the BTKis, acalabrutinib has the lowest rate of off-target effects and the highest selectivity.[5] Acalabrutinib is rapidly absorbed and has a short oral half-life of approximately 1.6 hours in healthy individuals and 0.6 hours in patients with mantle cell lymphoma.[7,8] In addition, acalabrutinib has an extended pharmacodynamic response, such that a 100 mg dose of acalabrutinib every 12 hours led to a median BTK occupancy of 97% to 99% in circulating blood mononuclear cells, which was maintained over the 12-hour period.[9] Acalabrutinib received approval for the treatment of patients with treatment-naive and relapsed/refractory CLL in the United States in November 2019 and in Europe in November 2020. These approvals were based on the results of 2 phase III studies: ELEVATE-TN and ASCEND.[10,11] Of note, acalabrutinib was available in 2 forms: capsules and tablets, with a recommended dosage of 100 mg taken orally every 12 hours, and treatment is continued until disease progression or unacceptable toxicity is encountered. However, the distribution of acalabrutinib capsules was discontinued in France in December 2023 and switched to tablets, which have a lower dependency on gastric pH.

In the ELEVATE-TN and the ASCEND trials, the most common adverse events (AEs) ($\geq$ 10%) of any grade observed with acalabrutinib monotherapy included headache, diarrhea, fatigue, arthralgia, cough, upper respiratory tract infection, rash, anemia, and neutropenia.[10,11] Atrial fibrillation (AF) was reported in $\leq$ 5% of patients receiving acalabrutinib monotherapy.[10,11] Similarly, in the ELEVATE-TN trial, 4% of patients developed hypertension (2% grade 3), and in the ASCEND trial, 3% developed hypertension (2% grade 3).[12] In the pooled safety analysis of acalabrutinib monotherapy studies across mature B-cell malignancies, the most common AEs were headache (38%), diarrhea (37%), upper respiratory tract infection (22%), contusion/bruising (22%), nausea (22%), fatigue (21%), and cough (21%).[13] Overall, clinical experience has shown that AEs experienced by patients treated with acalabrutinib are generally mild and tend to diminish over time, and discontinuation of acalabrutinib therapy due to serious AEs is infrequent.[5] Nevertheless, managing AEs to ensure compliance with treatment is a key point in patient care pathway. Indeed, stopping acalabrutinib therapy within the first year in the frontline setting was associated with an increased risk of CLL-related mortality in the registration trial ELEVATE-TN.[10] Additionally, caution is advised when co-administering acalabrutinib with strong CYP3A inhibitors or inducers, which may affect acalabrutinib plasma concentrations.[4,7]

Even though BTKi guidelines exist,[14,15] practical differences between BTKis—such as drug interactions and tolerance—are not fully addressed. Consequently, a consensus on acalabrutinib use would provide valuable guidance to the medical community. To address this, a Delphi study involving hematologists, pharmacists, cardiologists, dermatologists, and nurse practitioners throughout France was conducted to establish consensus-based practical guidance on optimizing the management of AEs associated with acalabrutinib therapy in patients with CLL.

Materials and Methods

Study Design

A modified, 2-round, online Delphi study was performed between February 2023 and March 2024. The Delphi approach is a widely used, rigorous, and accepted method in healthcare for obtaining expert consensus through an iterative ranking process.[16] Since this study consisted of a clinical vignette-based survey of expert opinions with no patient involvement, ethical approval was not required.

Steering Committee and Expert Panel

A steering committee was first established, comprising 3 hematologists, 2 nurse practitioners, 1 hospital pharmacist, 1 onco-dermatologist, and 1 cardio-oncologist, all with experience in managing leukemias across France. This committee then purposefully selected the Delphi expert panel composed of 26 members, including 19 hematologists, 4 hospital pharmacists, and 3 nurse practitioners. The panelists were selected based on their extensive expertise in managing both BTKis and CLL. The panel was also selected in a way to represent the entire French territory, ensuring national coverage. Additionally, it encompassed members from various healthcare facilities, including university hospitals (n = 19), general public hospitals (n = 4), and comprehensive cancer centers (n = 3).

Delphi Process

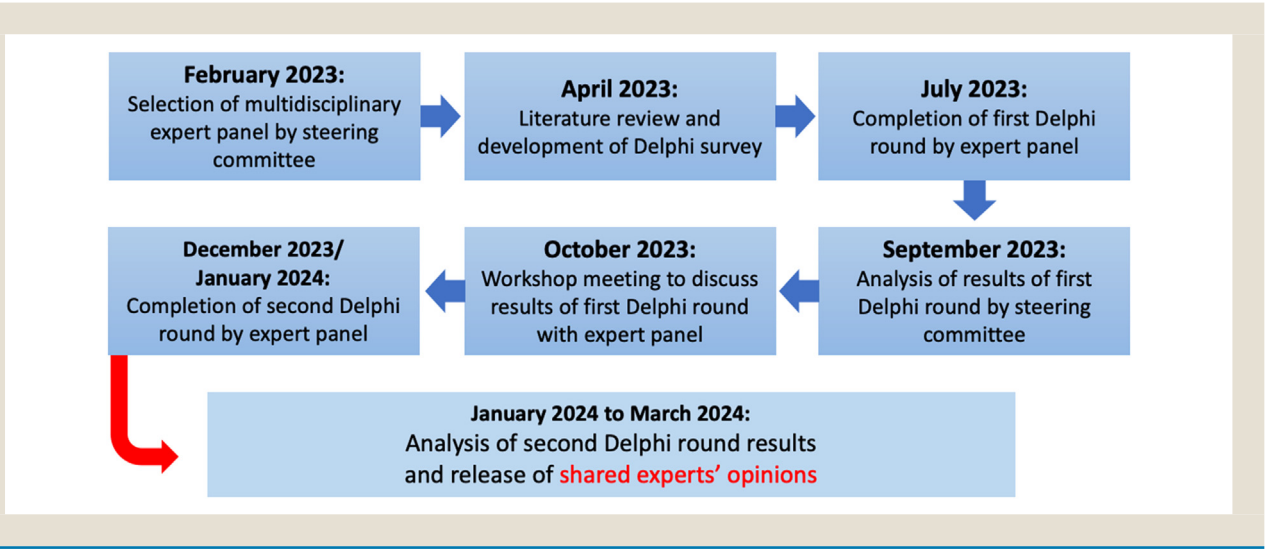
Figure 1 provides an overview of the Delphi consensus process. The modified Delphi process included 2 online survey rounds and a workshop meeting between these rounds. Based on clinical experience, a review of the literature on MEDLINE (via PubMed), and the prescribing information for acalabrutinib, the steering committee developed a survey questionnaire composed of a total of 89 items.

The survey was divided into 8 sections: (1) drug-drug and drug-food interactions of acalabrutinib; (2) headaches; (3) gastrointestinal AEs; (4) fatigue; (5) arthralgia and cramps; (6) dermatological AEs; (7) AF/cardiovascular AEs; (8) monitoring and routine care under acalabrutinib therapy. Panelists were asked to rate their agreement with each survey item on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Panelists were given 1 month to complete each round of the Delphi survey, and the responses of the expert panelists were anonymous in both Delphi rounds.

Between the first and second Delphi rounds, the steering committee convened a workshop meeting that brought together the expert panel to discuss the first Delphi round outcomes. Subsequent to this meeting, the Delphi survey was revised. Statements that lacked a consensus were rephrased to enhance clarity in the second round. Statements achieving consensus after the first Delphi round were removed from the second round. At the end of the Delphi process, a consensus-based expert opinion was provided.

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

Figure 1 Overview of the Delphi consensus process.



Analysis

The results of the 2 Delphi rounds were tabulated and presented through descriptive statistics. For each survey item in both rounds, the median score was calculated using cumulative relative frequency, as it allows visualizing the distribution of votes within the expert panel. Consensus in agreement was defined as a median score ≥ 4 with more than 75% of responses falling between 4 and 5 (agree/strongly agree). Conversely, consensus in disagreement was defined as a median score ≤ 2 with more than 75% of responses falling between 1 and 2 (strongly disagree/disagree).

Results

All 26 expert panelists completed the first round of the Delphi survey, and 25 completed the second round. In the first round, consensus was reached on 32 out of 89 survey items (36%). After the second round, 55 out of 78 items (71%) achieved consensus.

Drug-Drug and Drug-Food Interactions of Acalabrutinib

Consensus was reached (84% agreement, median score of 5) that an analysis of drug interactions by a hospital pharmacist is recommended before starting treatment with acalabrutinib. Overall, 76% of panelists agreed that acalabrutinib does not present a different drug interaction profile compared to other BTKis. In addition, 88% of panelists did not advocate for pharmacological monitoring of its dosage if a drug interaction is suspected while taking acalabrutinib. Similarly, 76% of panelists did not recommend monitoring acalabrutinib dosage in case of a severe AE while on acalabrutinib treatment. The expert panel's recommendations regarding the use of acalabrutinib with CYP3A inhibitors and inducers, as well as gastric acid reducing agents are summarized in Table 1.

Headaches

The panel achieved consensus (92% agreement, median score of 5) that patients should be informed before starting acalabrutinib about the risk of headaches, which typically occur during the first month of treatment. Panelists recommended, with an 88% agreement and a median score of 4, the use of paracetamol in combination with caffeine in case of grade ≥ 2 headaches under acalabrutinib treatment. Importantly, 81% of panelists (median score of 4) recommended avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) due to their risk of bleeding. However, there was no agreement on whether a dose adjustment of acalabrutinib is needed in patients experiencing headaches.

Gastrointestinal Adverse Events

The panel agreed (92%, median score of 5) that no prophylaxis for gastrointestinal AEs in patients candidate to acalabrutinib therapy is indicated. In case of grade 2 nausea observed with acalabrutinib treatment, prescribing antiemetics was recommended, with a 96% agreement and a median score of 4. Recommendations for the management of diarrhea associated with acalabrutinib therapy, according to the expert panel, are presented in Table 2.

Fatigue

For patients experiencing grade 1 or 2 fatigue while being treated with acalabrutinib, 96% of panelists (median score of 4) advocated engaging in an adapted physical activity program. Overall, 88% of panelists (median score of 5) did not recommend dose adjustment as a first-line intervention in case of grade 1 or 2 fatigue.

Arthralgia and Cramps

Before initiating treatment with acalabrutinib, over 90% of panelists (median score of 5) advised informing the patient about the risk of arthralgia and cramps, which are generally of grade 1 or 2 in severity and typically occur during the first year of acalabrutinib treatment. According to 92% of panelists (median score of 4), analgesics are the recommended first-line treatment of grade 1 or 2 arthralgia or cramps observed with acalabrutinib therapy. In case of grade ≥ 3 arthralgia or cramps, and in the absence of improvement with first-line analgesics, 88% of panelists (median score of 4) recommended adjustment of acalabrutinib treatment.

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

Table 1 Use of Acalabrutinib With CYP3A Inhibitors or Inducers and Gastric Acid Reducing Agents According to the Expert Panel

	Co-Administered Product	Expert Opinion on Use of Acalabrutinib
CYP3A inhibitors	Weak CYP3A inhibitors (eg, amlodipine, ranitidine, azithromycin)	No dose adjustment
	Moderate CYP3A inhibitors (eg, ciprofloxacin, aprepitant, amiodarone, fluconazole, diltiazem)	No dose adjustment, but patients should be closely monitored
	Strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole, itraconazole, ritonavir, cobicistat)	Consider an alternative to acalabrutinib If strong CYP3A4 inhibitors will be used short-term (eg, anti-infectives for $\leq$ 7 days), a temporary cessation of acalabrutinib is recommended
CYP3A inducers (eg, St John's wort)		Avoid the use of these CYP3A inducers
Gastric acid reducing agents	H2-receptor antagonists (eg, ranitidine, famotidine)	Delay the intake of acalabrutinib in its capsule form
	Antacids (eg, calcium carbonate)	Delay the intake of acalabrutinib in its capsule form
	Proton pump inhibitors (eg, omeprazole, rabeprazole)	Delay the intake of acalabrutinib

Table 2 Management of Diarrhea Associated With Acalabrutinib Therapy According to the Expert Panel

Grading	Signs or Symptoms	Management
Grade 1	< 4 stools per day	• Stool culture • Food hygiene interventions
Grade 2	4-6 stools per day	• Stool culture • Symptomatic treatment (eg, loperamide)
Grade 3	• $\geq$ 7 stools per day • Rectal bleeding, fever, systemic hypotension	• Stool culture • Hospitalization • Discontinue acalabrutinib until diarrhea resolves
Grade 4	Life-threatening	• Stool culture • Hospitalization • Discontinue acalabrutinib until diarrhea resolves

Dermatological Adverse Events

Overall, 77% of panelists did not recommend a systematic dermatological consultation, including screening for skin cancers, before initiating treatment with acalabrutinib. According to 80% of panelists, acalabrutinib treatment can even be prescribed in patients with a history of basal cell carcinoma or squamous cell carcinoma. However, before starting acalabrutinib therapy, each patient should be informed about the potential risk of dermatological AEs, such as rash, bruising, and ecchymoses (87% agreement, median score of 4). Consensus was reached among panelists (88%-92% agreement, median score of 4) that before performing an invasive dermatological procedure in an acalabrutinib-treated patient, acalabrutinib should be discontinued during the 4 days preceding the procedure and resumed 48 hours after the procedure in the absence of bleeding. However, such consensus was not reached for cutaneous biopsy.

If bruises or petechiae are observed in acalabrutinib-treated patients, 88–92% of panelists considered that acalabrutinib should not be withheld and its dose should not be reduced. Similarly, 79% of panelists did not recommend a dose reduction or discontinuation of acalabrutinib if nail changes are observed. The management of other dermatological AEs, as per the expert panel's agreement, is outlined in Figure 2.

Atrial Fibrillation/Cardiovascular Adverse Events

Approximately 80% of panelists did not consider it contraindicated to start acalabrutinib treatment in patients with current or previous AF (median score of 4). Additionally, in patients receiving direct oral anticoagulants, 79% of panelists did not oppose the initiation of acalabrutinib therapy. However, 79% opposed the initiation of acalabrutinib therapy in patients on aspirin in combination with platelet aggregation inhibitors like clopidogrel (median score of 4). There was no agreement on starting acalabrutinib in patients receiving low molecular weight heparin (LMWH) or vitamin K antagonists. The expert panel's recommendations regarding the cardiovascular measures to take before initiating acalabrutinib therapy are provided in Figure 3A. The management of cardiovascular AEs observed during acalabrutinib therapy, as per the expert panel's agreement, is outlined in Figure 3B. Importantly, the panel agreed on blood pressure measurement for patients treated with BTKis at every clinical visit. The panel also recommended weekly self-monitoring of blood pressure during the first 3 months following the

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

Figure 2 Management of dermatological adverse events observed with acalabrutinib therapy according to the expert panel.

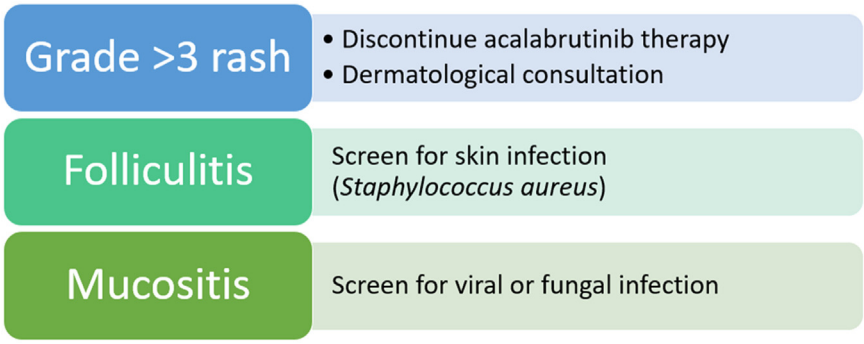
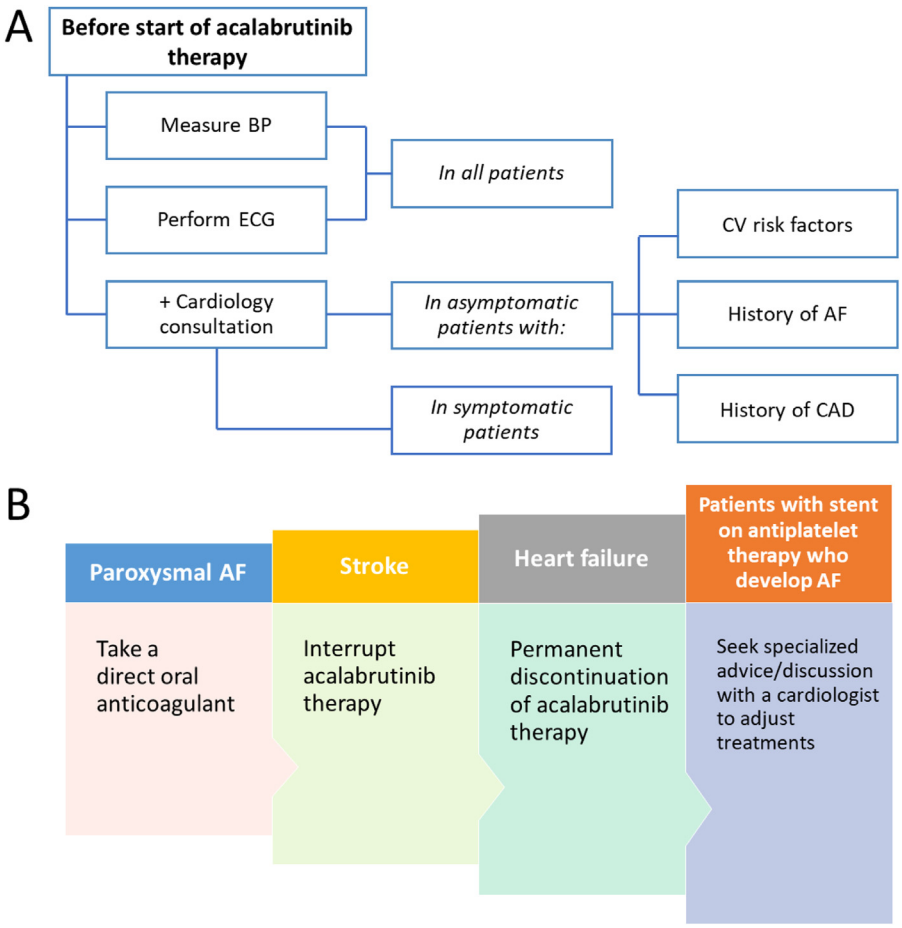
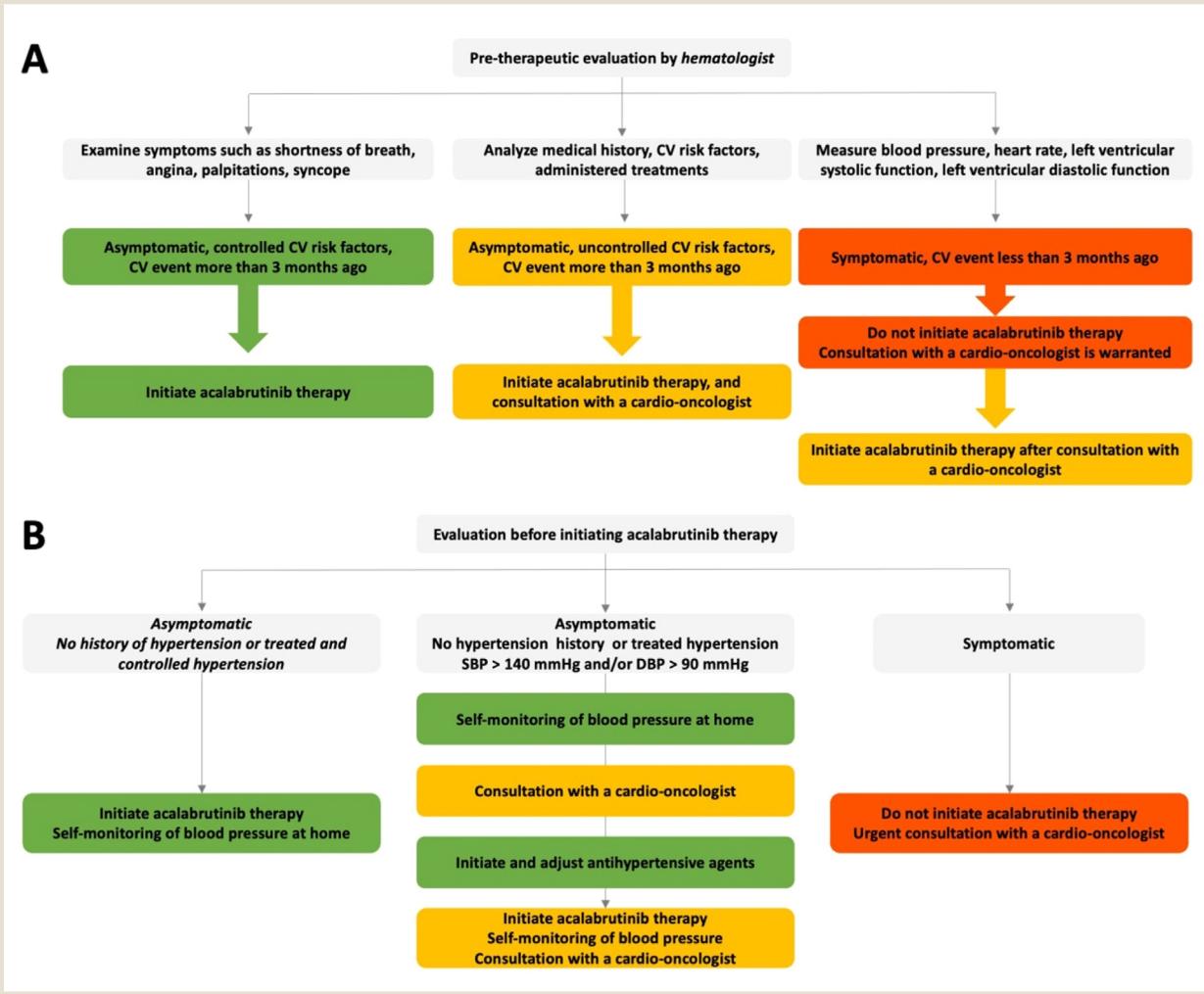


Figure 3 Cardiovascular measures to take before initiating acalabrutinib (A), and management of cardiovascular adverse events observed during acalabrutinib therapy (B), as per the expert panel. Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; ECG, electrocardiogram.



Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

Figure 4 Process to be followed, as per the expert panel, before initiating acalabrutinib therapy in patients without a history of hypertension (A) or with a history of hypertension or newly diagnosed hypertension (B). Abbreviations: CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure.



initiation of BTKis, and then monthly thereafter. An annual consultation with a cardio-oncologist was advised. The recommended process to be followed before initiating acalabrutinib therapy in patients without a history of hypertension, or with a history of hypertension or newly diagnosed hypertension, is presented in Figure 4.

Monitoring and Routine Care Under Acalabrutinib Therapy

Consensus was reached (96% agreement, median score of 4) that during acalabrutinib treatment, regular and multidisciplinary follow-up should be conducted. More than 80% of panelists (median score of 4) recommended that before dental procedures in a patient on acalabrutinib, acalabrutinib should be temporarily stopped for 4 days prior to the procedure and resumed 48 hours after the procedure in the absence of bleeding. This recommendation takes into account the short half-life of acalabrutinib.

Discussion

The present expert opinion, based on a Delphi method involving a multidisciplinary panel of hematologists, pharmacists, and nurses, is the first to establish consensus-based guidance for managing drug interactions and AEs associated with the second-generation BTKi acalabrutinib in patients with CLL. Data indicate that discontinuing BTKi treatment within the first year negatively impacts patient outcomes and leads to higher rates of AEs compared to nondiscontinuers.[17] Therefore, optimal management of AEs associated with BTKis is essential to prevent treatment discontinuation and maximize efficacy.

Previous research has consistently shown that a multidisciplinary approach, involving pharmaceutical care, contributes to delaying treatment failure and reducing drug interactions and severe toxicities in patients with B-cell malignancies receiving ibrutinib.[18] By leveraging a collaborative process with regular expert meetings, this study aims to reduce potential AEs and optimize the benefit-risk

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

ratio of acalabrutinib therapy in patients with CLL. Patient engagement is paramount in such process, as their active participation helps identify and promptly report any symptoms or AEs associated with acalabrutinib, thereby facilitating early intervention. Concurrently, treating physicians play a critical role by providing vital information about the risks and benefits of acalabrutinib therapy, monitoring for AEs, and making informed treatment adjustments based on individual patient needs and responses.

Overall, through the implementation of such a collaborative process, we can strive to enhance the safety profile of acalabrutinib, which has already shown better tolerability compared to ibrutinib.[19] Indeed, a head-to-head comparison of acalabrutinib and ibrutinib, in patients with previously treated CLL, showed a notable difference in toxicity.[19] Patients treated with ibrutinib experienced higher rates of diarrhea (46.0% vs. 34.6%), AF (16.0% vs. 9.4%), hypertension (23.2% vs. 9.4%), and bleeding events (51.3% vs. 38.0%) compared to those treated with acalabrutinib. Additionally, discontinuations due to AEs were higher with ibrutinib (21.3%) compared with acalabrutinib (14.7%).[19] This more favorable safety profile of acalabrutinib compared to ibrutinib may be attributed to its lack of irreversible targeting of alternative kinases, such as epidermal growth factor receptor (EGFR), interleukin-2-inducible T-cell kinase (ITK), and T-cell X-chromosome kinase (TXK).[8,20] Moreover, acalabrutinib has less effect on platelet aggregation, especially when antiaggregants are co-administered, due to decreased "on-target" Tec tyrosine kinase inhibition and the absence of pp60 Src kinase inhibition, whereas diminished platelet aggregation was observed with ibrutinib.[20-22] This pharmacologic characteristic may explain the more frequent mild bleeding events observed with ibrutinib compared to acalabrutinib, despite the low percentage of severe bleedings observed with both medications.[20-22]

Although there is no head-to-head comparison between second-generation BTKis, acalabrutinib demonstrated a lower odds ratio (OR) for several AEs.[23,24] In a matching-adjusted indirect comparison of acalabrutinib versus zanubrutinib in relapsed or refractory CLL, the risk of experiencing a serious AE (OR, 0.61; 95% confidence interval [CI], 0.39-0.97), an AE leading to dose reduction (OR, 0.30; 95% CI, 0.14-0.67), any grade hemorrhage (OR, 0.54; 95% CI, 0.34-0.87), or hypertension (any grade: OR, 0.18; 95% CI, 0.09-0.37; grade $\geq$ 3: OR, 0.22; 95% CI, 0.09-0.54) was lower with acalabrutinib compared to zanubrutinib.[23] Similarly, in another unanchored matching-adjusted indirect comparison in patients with treatment-naive CLL, the risk of experiencing hypertension was significantly lower with acalabrutinib versus zanubrutinib (OR, 0.44; 95% CI, 0.20-0.99). There was no evidence of a difference in the odds of having AF/atrial flutter (OR, 1.69; 95% CI, 0.66-4.36) with acalabrutinib versus zanubrutinib.[24]

Systemic hypertension is a widely recognized AE of BTKi use that often occurs late in the span of therapy, and has the potential to cause major adverse cardiovascular events (MACE) if not treated appropriately.[25] In a retrospective analysis from the United States of 280 acalabrutinib-treated patients with CLL, 59.2% developed new or worsened hypertension over a median of 41 months, with a mean increase in systolic blood pressure (SBP) of 7.2 mmHg.[26] This translated into an observed incidence of new hypertension of 205 per 1000 person-years for acalabrutinib, compared to 312 per 1000 person-years for ibrutinib. Multivariable predictors for the development of new or worsened hypertension included African American ethnicity (hazard ratio [HR], 4.35; 95% CI, 1.21-15.63; $P = .024$), prior AF (HR, 1.63; 95% CI, 1.06-2.49; $P = .025$), and body mass index (HR, 1.05; 95% CI, 1.02-1.09; $P = .005$).[26] For every 5 mmHg SBP increase, there was a 27% increase in MACE risk ($P < .001$), and a 42% increase in the risk for AF development ($P < .001$). There was nevertheless no difference in the risk of MACE between patients with new or worsened hypertension and those with no or stable hypertension (HR, 1.12; $P = .75$).[26]

However, in a cumulative analysis of 11 clinical trials investigating the prevalence of hypertension in patients with CLL who received acalabrutinib, acalabrutinib monotherapy did not worsen pre-existing hypertension or increase the risk of new-onset hypertension.[27] This finding is reassuring, given that systemic hypertension is a common condition among the CLL patient population, many of whom are older and may already be managing multiple comorbidities.[27] In practice, this may encourage hematologists to consider acalabrutinib as a preferable treatment option for patients with CLL who either have a history of hypertension or are at risk of developing this condition.

Nevertheless, in line with the joint guidelines from various European scientific societies,[28] the panelists agreed on measuring blood pressure at every clinical visit for patients treated with BTKis. The expert panelists also adhered to the recommendations recently published by Quatermaine and colleagues.[6] Importantly, patients should be educated to self-monitor their blood pressure with 3 consecutive morning and evening measurements over 3 days.[29] Weekly home monitoring of blood pressure during the first 3 months and every month thereafter should be considered for patients treated with BTKis.[6,28] According to the recommendations by Quatermaine and colleagues, dihydropyridines are the preferred first-line agents of BTKi-associated hypertension due to their relatively minimal side effects.[6] Medications that inhibit or interact with the CYP3A4 metabolism pathway, such as diltiazem and verapamil, should be limited as treatment options for hypertension, because their inhibition of CYP3A4 may lead to increased therapeutic levels of acalabrutinib.[6] Furthermore, given that 1 out of every 16 newly diagnosed patients with CLL has a history of AF, monitoring for AF is recommended for patients receiving BTKis.[15,30] Clinical practice guidelines from Europe also recommend opportunistic screening for AF by pulse-taking and/or electrocardiogram rhythm strip at every clinical visit during BTKi therapy.[28]

To mitigate the risk of bleeding, BTKi-treated patients should be cautioned against using NSAIDs and aspirin. If dual antiplatelet therapy is indicated, consideration should be given to replacing any BTKi with a different agent.[21] The panelists concur with such caution and additionally advocate that before performing an invasive dermatological procedure or dental procedures in an acalabrutinib-treated patient, acalabrutinib should be discontinued during the 4 days preceding the procedure and resumed 48 hours after the procedure in the absence of bleeding. However, our expert-based guidance did not oppose the initiation of acalabrutinib in patients on direct oral anticoagulants, though there was some uncertainty regarding those receiving LMWH or warfarin.

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

Among all acalabrutinib-related AEs, headache is the most common and the most specific AE, experienced by up to 40% of patients receiving acalabrutinib therapy.[10,11,19] However, over 95% of acalabrutinib-related headaches are classified as grade 1 or 2.[13] The mechanism for acalabrutinib-related headaches is unclear, but could include calcitonin gene-related peptide agonism.[4] Likewise, fatigue, often reported by patients taking BTKis, is multifactorial, potentially linked to anemia restoration, reduction of tumor size, and overall management of CLL symptoms.[31] Acalabrutinib-related headaches usually occur early in the treatment course, typically resolve after 1 to 2 months of therapy initiation, and generally can be managed with analgesics (eg, paracetamol) and caffeine supplements without the need for dose alterations.[4,15,32] The Delphi expert panel concurred with this treatment approach, and confirmed that patient education prior to initiation of acalabrutinib therapy helps to reassure the patient that headache is not a long-term consequence.[4] Likewise, patient education on the characteristic dermatological AEs of acalabrutinib such as bruising, ecchymoses, petechiae, as well as skin infections like *Staphylococcus aureus* superinfection is warranted.[33]

The panelists suggest that before starting treatment with acalabrutinib, an analysis of drug interactions by a hospital pharmacist is to be undertaken. Indeed, before initiating acalabrutinib therapy, it is essential to compile a list of concomitant medications to anticipate potential drug-drug interactions and optimize the clinical benefits of acalabrutinib for each patient.[34] Acalabrutinib is primarily metabolized by CYP3A.[7] In a physiologically-based pharmacokinetic model, the strong CYP3A inhibitor itraconazole increased acalabrutinib area under the curve by 5.21-fold, and the strong CYP3A inducer rifampicin decreased acalabrutinib area under the curve to 0.23-fold of that when administered alone.[35] Hence, the current label of acalabrutinib highlights avoiding its concomitant use with strong CYP3A inhibitors due to an increased risk of toxicity and with strong CYP3A inducers due to potential efficacy concerns.[36]

In another pharmacokinetic study, acalabrutinib total active moiety exposure increased by less than 2-fold when co-administered with moderate CYP3A inhibitors fluconazole and isavuconazole, suggesting that no dose reduction is needed when acalabrutinib is used with moderate CYP3A inhibitors.[7] The selection of moderate CYP3A inhibitors may be justified in the management of disease-related and acalabrutinib-related infections to minimize the necessity of dose modifications.[7] Given that infections in BTKi-treated patients are common, stool samples for common pathogens should be tested in case of acalabrutinib-related diarrhea to rule out infection.[37] Additionally, according to the current label of acalabrutinib, acalabrutinib tablets can be co-administered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids), unlike acalabrutinib capsules, which show impaired uptake when given with acid reducing agents.[37]

An important objective of this Delphi study was to obtain consensus from a diverse and representative panel of experts in CLL. However, we acknowledge that our study is based on the input of specific individual expert panelists in France, and may not represent global perspectives. In addition, the Delphi process lacks generally accepted criteria for consensus.[38]

Conclusions

While acalabrutinib features a favorable safety profile, proactively anticipating and mitigating its AEs is essential to prevent their occurrence or to minimize their impact. Our Delphi study highlights the power of a collaborative process in enhancing the management of acalabrutinib-associated AEs through consensus-based guidance. These findings enhance existing clinical guidelines by providing valuable expert insights into the prevention and mitigation of potential side effects in routine clinical practice. To truly optimize this approach, it is paramount to engage patients, caregivers, and the entire multidisciplinary team, ensuring comprehensive and effective care. Moreover, implementing a structured outpatient follow-up is warranted for closely monitoring patients at the initiation of acalabrutinib treatment.

Disclosure

LY received consulting fees from AbbVie, AstraZeneca, BeiGene, BMS/Celgene, Gilead/Kite, Janssen, and Roche. SE received consultancy fees from Amgen, AstraZeneca, Bayer, BMS, Eisai, Leo Pharma, and Pierre Fabre. VL received honoraria from AbbVie, AstraZeneca, and BeiGene. VS received consulting fees from Novartis, BMS, MSD, Pierre Fabre, AstraZeneca, Janssen, Bayer, and Immunocore. CT received consulting fees from AbbVie, AstraZeneca, Beigene, and Janssen. The other authors do not report any conflicts of interest.

CRediT authorship contribution statement

Loïc Ysebaert: Investigation, Supervision, Writing – original draft, Writing – review & editing. **Stéphane Ederhy:** Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Véronique Leblond:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Stéphanie Malartre:** Investigation, Validation. **Anaïs Portalier:** Investigation, Validation. **Vincent Sibaud:** Investigation, Validation, Writing – original draft. **Cécile Tomowiak:** Investigation, Validation, Writing – original draft. **Jérémie Zerbit:** Investigation, Validation, Writing – original draft.

Data Availability Statement

Data supporting the findings of this study are available on request from the corresponding author.

Acknowledgments

The authors would like to thank Thomas Rohban, MD, and Magalie El Hajj, PharmD, of Partner 4 Health (Paris, France) for providing medical writing support in accordance with current Good Publication Practice guidelines. The authors also thank RE-IMAGINE Health Agency (Paris, France); and Sandy Azzi-Hatem, PhD, from AstraZeneca (Paris, France) for their contributions. The study was funded by AstraZeneca, France.

References

1. Tse E, Kwong YL, Goh YT, et al. Expert consensus on the management of chronic lymphocytic leukaemia in Asia. *Clin Exp Med.* 2023;23(6):2895–2907.

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013

2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12–49.
3. Quinquenel A, Aurran-Schleinitz T, Clavert A, et al. Diagnosis and treatment of chronic lymphocytic leukemia: recommendations of the French CLL Study Group (FILO). *Hemasphere*. 2020;4(5):e473.
4. O'Brien SM, Brown JR, Byrd JC, et al. Monitoring and managing BTK inhibitor treatment-related adverse events in clinical practice. *Front Oncol*. 2021;11:720704.
5. Kuss B, Nagarajan C, Hsieh WS, Cheah CY. Practical management of chronic lymphocytic leukemia with acalabrutinib. *Leuk Lymphoma*. 2022;63(12):2785–2794.
6. Quartermaine C, Ghazi SM, Yasin A, et al. Cardiovascular toxicities of BTK inhibitors in chronic lymphocytic leukemia: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol*. 2023;5(5):570–590.
7. Chen B, Zhou D, Wei H, et al. Acalabrutinib CYP3A-mediated drug-drug interactions: clinical evaluations and physiologically based pharmacokinetic modelling to inform dose adjustment strategy. *Br J Clin Pharmacol*. 2022;88(8):3716–3729.
8. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther*. 2017;363(2):240–252.
9. Byrd JC, Woyach JA, Furman RR, et al. Acalabrutinib in treatment-naive chronic lymphocytic leukemia. *Blood*. 2021;137(24):3327–3338.
10. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet*. 2020;395(10232):1278–1291.
11. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2849–2861.
12. Awan FT, Addison D, Alfraih F, et al. International consensus statement on the management of cardiovascular risk of Bruton's tyrosine kinase inhibitors in CLL. *Blood Adv*. 2022;6(18):5516–5525.
13. Furman RR, Byrd JC, Owen RG, et al. Pooled analysis of safety data from clinical trials evaluating acalabrutinib monotherapy in mature B-cell malignancies. *Leukemia*. 2021;35(11):3201–3211.
14. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(1):23–33.
15. Wierda WG, Byrd JC, Abramson JS, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 4.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2020;18(2):185–217.
16. Jandhyala R. Delphi, non-RAND modified Delphi, RAND/UCLA appropriateness method and a novel group awareness and consensus methodology for consensus measurement: a systematic literature review. *Curr Med Res Opin*. 2020;36(11):1873–1887.
17. Huntington SF, de Nigris E, Puckett JT, et al. Real-world analysis of adverse event rates after initiation of ibrutinib among medicare beneficiaries with chronic lymphocytic leukemia. *Cancer Med*. 2024;13(2):e6953.
18. Zerbit J, Chevret S, Bernard S, et al. Improved time to treatment failure and survival in ibrutinib-treated malignancies with a pharmaceutical care program: an observational cohort study. *Ann Hematol*. 2020;99(7):1615–1625.
19. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase iii trial. *J Clin Oncol*. 2021;39(31):3441–3452.
20. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323–332.
21. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. *J Thromb Haemost*. 2017;15(5):835–847.
22. Series J, Garcia C, Levade M, et al. Differences and similarities in the effects of ibrutinib and acalabrutinib on platelet functions. *Haematologica*. 2019;104(11):2292–2299.
23. Skarbnik A, Kittai A, Miranda M, et al. P642: a matching-adjusted indirect comparison of the efficacy and safety of acalabrutinib versus zanubrutinib in relapsed or refractory chronic lymphocytic leukemia. *HemaSphere*. 2023;7:e4236347.
24. Kittai AS, Allan JN, James D, et al. An indirect comparison of acalabrutinib with and without obinutuzumab vs zanubrutinib in treatment-naive CLL. *Blood Adv*. 2024;8(11):2861–2869.
25. Samples L, Voutsinas J, Fakhri B, et al. Hypertension treatment for patients receiving ibrutinib: a multicenter retrospective study. *Blood Adv*. 2024;8(9):2085–2093.
26. Chen ST, Azali L, Rosen L, et al. Hypertension and incident cardiovascular events after next-generation BTKi therapy initiation. *J Hematol Oncol*. 2022;15(1):92.
27. Ferrajoli A, Follows G, Marmor Y, et al. Cumulative review of hypertension in patients with Chronic Lymphocytic Leukemia (CLL) and other hematologic malignancies treated with acalabrutinib. *Blood*. 2023;142(Supplement 1):1917–1918.
28. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229–4361.
29. Hodgkinson JA, Stevens R, Grant S, et al. Schedules for self-monitoring blood pressure: a systematic review. *Am J Hypertens*. 2019;32(4):350–364.
30. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). *Leuk Lymphoma*. 2017;58(7):1630–1639.
31. Wan Q, Li Q, Lai X, Xu T, Hu J, Peng H. Data mining and safety analysis of BTK inhibitors: a pharmacovigilance investigation based on the FAERS database. *Front Pharmacol*. 2022;13:995522.
32. Banerji V, Aw A, Robinson S, Doucette S, Christofides A, Sehn LH. Bruton tyrosine kinase inhibitors for the frontline treatment of chronic lymphocytic leukemia. *Curr Oncol*. 2020;27(6):e645–e655.
33. Sibaud V, Beylot-Barry M, Protin C, Vigarios E, Recher C, Ysebaert L. Dermatological toxicities of bruton's tyrosine kinase inhibitors. *Am J Clin Dermatol*. 2020;21(6):799–812.
34. Gribben JG, Bosch F, Cymbalista F, et al. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. *Br J Haematol*. 2018;180(5):666–679.
35. Zhou D, Podoll T, Xu Y, et al. Evaluation of the drug-drug interaction potential of acalabrutinib and its active metabolite, ACP-5862, using a physiologically-based pharmacokinetic modeling approach. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(7):489–499.
36. European Public Assessment Report. Calquence : EPAR - Product information. 2024; https://www.ema.europa.eu/en/documents/product-information/calquence-epar-product-information_en.pdf. Accessed July 8, 2024.
37. Stephens DM, Byrd JC. How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood*. 2019;133(12):1298–1307.
38. Powell C. The Delphi technique: myths and realities. *J Adv Nurs*. 2003;41(4):376–382.

Please cite this article as: Loïc Ysebaert et al, Expert Opinion on Managing Adverse Reactions Associated With Acalabrutinib Therapy: A Delphi Consensus From France, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2024.10.013