Observational Plan

Title	A non-interventional, prospective, open-label, observational study evaluating the effectiveness and safety of acalabrutinib (Calquence®) in patients with chronic lymphocytic leukemia (CLL) receiving direct oral anticoagulation (DOAC).
Authors	[redacted]
Protocol-No.	IOM-100473
Version-No.	1.0
Document status	Final
Release date	2022-06-27
Scientific leader	[redacted]
Sponsor	iOMEDICO Freiburg, Germany
Coordination	iOMEDICO Freiburg, Germany

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Amendments to the Observational Plan

Number	Date	Version Number	Summary of Changes

Key Responsibilities

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Sponsor	iOMEDICO	
Scientific Leader	Ambulantes Krebszentrum	
Medical Manager	iOMEDICO	
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Clinical Data Manager	iOMEDICO	
Pharmacovigilance Reporting	AstraZeneca	

Approval Page

I have read, understood and reviewed the observational plan entitled “CICERO”; Version 1.0 Date 27-06-2022.

I agree, approve it and undertake to comply with it. I agree to comply with the safety reporting procedures.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the non-interventional study without the prior written consent of the sponsor. The observational plan may not be divulged, published, presented or otherwise disclosed without prior consent of iOMEDICO (sponsor).

Scientific Leader:

Date	[redacted]

Sponsor:

Date	[redacted] iOMEDICO AG
Date	[redacted] iOMEDICO AG
Date	[redacted] iOMEDICO AG

Observational Plan Summary (English)

Sponsor Protocol Identifier	IOM-100473
Official Title	A non-interventional, prospective, open-label, observational study evaluating the effectiveness and safety of acalabrutinib (Calquence®) in patients with chronic lymphocytic leukemia (CLL) receiving direct oral anticoagulation (DOAC).
Brief Title/ Study Acronym	Acalabrutinib in patients with chronic lymphocytic leukemia with direct oral anticoagulation (CICERO).
Study Sponsor	iOMEDICO
Scientific Leader	[redacted]
Study Design	This is a prospective, observational, multicenter, non-interventional, cohort study in patients with CLL in need of treatment and co-medication with DOAC (i.e., edoxaban, rivaroxaban, dabigatran and apixaban) for concomitant disease. The implementation of this non-interventional study (NIS) does not influence the physician's decision regarding therapeutic strategy, diagnostic methods, frequency of medical examinations and other procedures during and after the treatment. All data will be obtained in routine clinical practice.
Indication	Adult patients (≥18 years) with previously untreated or treated CLL and co-medication with DOAC and treatment decision for acalabrutinib (Calquence®).
Study Treatment	Acalabrutinib (Calquence®) +/- obinutuzumab (Gazyvaro®), according to current Summary of Product Characteristics (SmPC)
Planned Number of Patients and Study Sites	50 patients (excluding screening failures and patients with off-label use or violation of inclusion / exclusion criteria identified after treatment start) 20 (hematological and/or oncological sites (office-based hematologists and medical oncologists, hematology/oncology outpatient-centers, (university) hospitals in Germany)
Study Rationale	Chronic lymphocytic leukemia (CLL) is the most common hematological malignancy in the western hemisphere, accounting for nearly 25% of all leukemias. The median age at time of diagnosis is >70 years, with more than 70% of patients being older than 65 years.[1,2] Elderly CLL patients often suffer from multiple cardiovascular comorbidities including atrial fibrillation (AF), deep vein thrombosis (DVT) or pulmonary embolism (PE) which make anticoagulation mandatory.[3] Additionally ischemic strokes occur in 80% of the elderly patients, that may also lead to initiation of secondary prophylaxis with anticoagulating agents.[4] The management of cardiovascular comorbidities represents a major challenge in patients with CLL, Several drugs are available for anticoagulation including vitamin K antagonists (VKAs), unfractionated heparin and low-molecular-weight heparins. Recently, new direct oral anticoagulants (DOAC), i.e., factor Xa inhibitors (edoxaban, rivaroxaban, apixaban) or thrombin-inhibitors (e.g., dabigatran) have become available and extend treatment options. In cancer patients, venous

	thromboembolism (VTE) treatment is associated with increased risk of bleeding complications and must be monitored carefully.[5] The rate of major bleeding events in cancer patients treated with edoxaban was 6.9% in the HOKUSAI trial (NCT02073682)[6], whereas in non-cancer patients with atrial fibrillation receiving dabigatran, the rate of major bleeding events was around 3.7%.[7] Clinical course of CLL is heterogenous. Most patients are asymptomatic and do not require active treatment. However, other patients suffer from organ involvement, i.e. lymphadenopathy and/or hepatosplenomegaly or B symptoms like persistent fever, night sweats and/or unintentional weight loss as well as fatigue.[2] Indication for treatment is mainly based on symptoms, complete blood cell count and physical examination.[2] Response to treatment should be assessed according to the International Workshop of CLL guidelines.[8] Treatment of CLL is usually not curative, but patients can achieve remissions and long-term stabilization of their disease. However, most patients eventually relapse. Several treatment strategies are available for CLL including conventional chemotherapy combined with anti-CD20 monoclonal antibodies. Type of treatment, especially in first line, is based on clinical fitness and genetic alterations (e.g., *TP53*) of the CLL clone. Current treatment guidelines recommend treatment of newly diagnosed CLL in patients with Binet stage C and stage B or A with additional fulfilled criteria (e.g., massive splenomegaly or lymphadenopathy).[9] For patients with no *TP53* mutation or complex karyotype, a Bruton kinase inhibitor (BTKi) as monotherapy or in combination with an anti-CD20 antibody or chemotherapy (fludarabine, cyclophosphamide, rituximab (FCR) regimen) or venetoclax in combination with obinutuzumab is recommended as first-line treatment. For elderly and comorbid patients instead of FCR, bendamustine + rituximab or chlorambucil + obinutuzumab is recommend in the first line. For patients with a *TP53* mutation or complex karyotype a BTKi as monotherapy or in combination with an anti-CD20 antibody or venetoclax in combination with obinutuzumab is the recommended first-line treatment. As second-line therapy a BTKi or venetoclax in combination with rituximab is recommended, depending on the response to first-line treatment and disease characteristics.[9] In addition, there is no standard combination therapy for patients with relapsed CLL. Therefore, there is an urgent medical need to identify new strategies.[1] BTKis as ibrutinib or acalabrutinib have shown high efficacy in nearly all subgroups and have therefore become standard treatment for the majority of patients, despite subgroups as age or risk groups.[10,11] Treatment-naïve (TN) and relapsed/refractory (R/R) CLL patients showed an overall response rate (ORR) of 88% and 87%, respectively, when treated with ibrutinib.[10,12] TN patients treated with zanubrutinib, a BTKi not yet approved, showed an ORR of 94.5% in an early clinical study.[13,14] Acalabrutinib treated patients showed an ORR of 80% in R/R CLL and 86%-95% in TN CLL.[11,15] Early clinical studies have shown a greater bleeding risk in patients treated with BTKis.[10,11,15] Any grade hemorrhages were found in ~48% of patients treated with ibrutinib or zanubrutinib, resepcitvely.[10,13] In patients treated with acalabrutinib monotherapy or combinatorial therapy, the rate was lower with ~30%. Grade ≥3 hemorrhage was found in 2-3% of patients treated with acalabrutinib. [11,15] Up to now, no prospective data exist showing interactions of BTKis and DOACs. A retrospective cohort study evaluated the risk of major bleeding events in 30 patients with B-cell lymphoma treated with ibrutinib and DOACs. Major bleeding events, defined as grade 3 or 4, were detected in 16.6% of patients.[16] Nevertheless, in Germany, a majority of physicians is reluctant in the usage of BTKis in patients undergoing comedication with DOACs, therefore denying these

	patients an effective and otherwise safe treatment and have to choose from other, potentially less tolerable treatment options like e.g. FCR. The goal of CICERO is to investigate the clinical outcome with a particular focus on prospective data on safety using acalabrutinib (+/- obinutuzumab) in CLL patients receiving co-medication with DOACs (edoxaban, rivaroxaban, dabigatran, apixaban) irrespective of treatment line.

Objectives and Endpoints	The objective of this NIS is to evaluate safety with the focus on bleeding events in adult patients with CLL receiving acalabrutinib (+/- obinutuzumab) and co-medication with DOAC in a real-world setting.
	• Assess bleeding events in patients receiving acalabrutinib and concomitant treatment with DOAC
	  • Incidence proportion of major bleeding events according to Schulman et al.[17] (primary endpoint)
	  • Incidence proportion of clinically relevant non-major (CRNM) bleeding events (key secondary endpoint)
	  • Incidence proportion of major (according to Schulman et al.[17]) and/or CRNM bleeding events (key secondary endpoint)
	  • Incidence proportion of major bleeding according to Ghia et al.[15] (key secondary endpoint)
	  • Incidence proportion of any bleeding event (secondary endpoint)
	  • Time to first occurrence of major (according to Schulman et al.[17]) bleeding events (secondary endpoint)
	  • Incidence proportion of central nervous system (CNS) bleeding events (secondary endpoint)
	• Assess safety in patients receiving acalabrutinib and concomitant treatment with DOAC (secondary objective)
	  • Mortality from all causes during acalabrutinib therapy
	• Assess safety in patients receiving acalabrutinib and concomitant treatment with DOAC in terms of interactions with effectiveness of DOAC (secondary objective)
	  • Rate of any new or recurrent ischemic stroke or arterial systemic embolism or venous thromboembolic events
	  • Rate of VTE-related death
	• Assess effectiveness of acalabrutinib in patients treated with a DOAC (secondary objective)
	  • ORR
	  • Progression-free survival (PFS)
	  • Overall survival (OS)
	• Assess parameters of acalabrutinib therapy decision making (secondary objective)
	  • Frequency of distinct parameters affecting therapy choice
	• Describe treatment in detail (secondary objective)
	  • Details of previous therapies
	  • Details of acalabrutinib (+/- obinutuzumab) treatment and treatment with DOAC

	• Frequency of concomitant medication other than DOAC
Inclusion Criteria	Patients must comply with all the following criteria to be enrolled in the study: • 18 years of age or older • Patients with chronic lymphocytic leukemia (CLL) and decision for treatment with acalabrutinib (+/- obinutuzumab) according to current SmPC as assessed by the treating physician or already started treatment with acalabrutinib (+/- obinutuzumab) according to current SmPC no longer than 6 weeks ago • Other concomitant disease resulting in medical need of or already under treatment with direct oral anticoagulant (DOAC) treatment with edoxaban (Lixiana®) or rivaroxaban (Xarelto®) or dabigatran (Pradaxa®) or apixaban (Eliquis®) according to the respective current SmPC. • Eastern Cooperative Oncology Group (ECOG) performance status 0-2 • Signed, written informed consent.
Exclusion Criteria	Patient is not eligible, if any of the following criteria is met: • Combination of acalabrutinib with other substances than obinutuzumab for CLL treatment • Participation in an interventional clinical trial with acalabrutinib
Effectiveness Assessments	Response of CLL and lymph nodes and/or potentially affected organs (i.e., liver, spleen) will be assessed and evaluated according to local medical standards recommended according to guidelines from start of acalabrutinib treatment until progressive disease (PD) of CLL or death, whatever comes first. Survival will be followed up for 12 months after last patient in (LPI).
Safety Assessments	As per clinical routine • Continuous recording and grading according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 of all adverse events (AEs) including serious adverse events (SAEs) after signature of informed consent form, during acalabrutinib treatment and 30 days after end of acalabrutinib treatment. (Neither patient-reported symptoms nor questionnaires will be checked for hidden AEs). For retrospectively included patients, all (S)AEs documented in the medical records that occurred from start of therapy until enrolment have to be reported additionally. • Monitoring of laboratory values (incl. tests on coagulation monitoring and platelet count/functional tests, if conducted in the clinical routine practice by the documenting study site).
Assessment of Patient-Reported Outcomes (PROs)	Participation of patients in the PRO module is not optional • Patient questionnaire for bleeding events adapted to the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool.[18–20] Questionnaires will be distributed by study site to the patient at every visit in routine care during treatment with acalabrutinib (+/- obinutuzumab). For retrospectively included patients, questionnaires will be additionally handed out

<table>
<tr><td></td><td>at inclusion. Patients will be asked if distinct events occurred in the time between the last visit in routine care until the current visit in routine care (or start of treatment until inclusion for retrospectively included patients at baseline) and will discuss the questionnaire with the physician to determine whether any AE occurred. This questionnaire will only be used as documentation aid and will not be transferred to the electronic case report form (eCRF) but is seen as source document. Distribution and fill-out date will be tracked in the eCRF.</td></tr>
<tr><td>Other assessments</td><td>• Details of prior treatment (including stem cell transplantations, radiotherapies and antineoplastic treatments) (Start/end dates / substances / transplantation type / mobilization / high dose therapy / PD with date of PD / reasons for end of treatment)
• Details of acalabrutinib treatment (including start/end date, dose, dose modifications with reasons, reasons for end of treatment)
• Details of obinutuzumab treatment (including start/end date, reasons for end of treatment)
• Details of DOAC treatment (including type of DOAC, start/end date, dose, dose modifications, reasons for treatment, reason for end of treatment)
• Details on surgeries or radiotherapies during acalabrutinib treatment (e.g., occurrence date, start/end date, indication)
• Physician’s treatment decision at baseline using a questionnaire with different factors potentially informing the treatment decision like e.g., age, comorbidities, guidelines
• Concomitant medication (substance, start/end date, reason for application) with focus on drugs for treatment of anemia, thrombocytopenia, diarrhea, emesis, infections as well as anti-coagulation drugs other than the DOAC</td></tr>
<tr><td>Statistics and Data Analysis</td><td>Sample size

Due to the exploratory character of the study, no formal sample size calculation is conducted, and no hypotheses will be tested. N=50 patients will be enrolled.

For the primary endpoint, i.e., incidence proportion of major bleedings, the following precision (95% confidence interval (CI)) can be reached with this sample size depending on the observed proportion of events:

<table>
<tr><th>Sample size</th><th>Proportion of patients with major bleeding</th><th>95% CI (exact Clopper-Pearson)</th></tr>
<tr><td>50</td><td>2%</td><td>0.05% - 10.65%</td></tr>
<tr><td>50</td><td>3%</td><td>0.22% - 12.22%</td></tr>
<tr><td>50</td><td>4%</td><td>0.49% -13.71%</td></tr>
<tr><td>50</td><td>5%</td><td>0.84% - 15.15%</td></tr>
</table>

Safety analyses

Incidence proportion of major bleeding according to Schulman et al. (frequencies): Bleeding is defined as major, if it is fatal (contributes to death) and/or symptomatic in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) and/or causing a decrease in hemoglobin of 2 g/dL</td></tr>
</table>

	(1.24 mmol/l) or more or requires a transfusion of 2 or more units of whole blood or red blood cells.[17] *Incidence proportion of CRNM bleeding events (frequencies):* CRNM bleeding is defined as bleeding that does not meet the criteria for major bleeding according to Schulman et al.[17] but is associated with the need for medical intervention and/or personal contact with a physician and/or hospitalization or increase in level of care.[21] *Incidence proportion of major (according to Schulman et al.) and/or CRNM bleeding events (frequencies).* *Incidence proportion of major bleeding according to Ghia et al. (frequencies):* Major bleeding is defined as any serious or grade ≥3 hemorrhage or CNS hemorrhage of any grade, excluding immune thrombocytopenic purpura.[15] *Incidence proportion of any bleeding event (frequencies).* *Time to first occurrence of major bleeding events according to Schulman et al.:* Competing risk analysis (competing event: death) will be conducted. *Incidence proportion of CNS bleeding events (frequencies)* *Incidence proportion of mortality from all causes:* Frequency of patients who deceased during acalabrutinib therapy or within 30 days after last dose. *Incidence proportion of VTE-related death (frequencies).* *Incidence proportion of any new or recurrent ischemic stroke or systemic arterial embolism or venous thromboembolic events (frequencies).* ***Effectiveness analyses*** *ORR (frequencies):* is defined as proportion of patients with any response (CR/PR) overall. *PFS:* is defined as time from start of acalabrutinib therapy to first occurrence of progressive disease or death from any cause, whichever comes first. It will be analyzed using Kaplan-Meier method. *OS:* is defined as time from start of acalabrutinib treatment to death from any cause. It will be analyzed using Kaplan-Meier method. ***Therapy decision*** *Therapy decision parameter:* Frequency of distinct parameters affecting therapy choice will be given. ***Treatment details***

	Frequency of previous therapies *Details of acalabrutinib treatment and treatment with DOAC (frequencies, descriptive statistics)* *Frequency of concomitant medication other than DOAC:* Frequencies and percentages of concomitant medication (anti-anemia, anti-thrombocytopenia, anti-coagulation, anti-emetic, anti-diarrhea, anti-infection, anti-hyperuricemia medication) will be given. ***Subgroups*** Effectiveness parameters (ORR, PFS, OS) will be analyzed in the subgroup of patients enrolled for first-line acalabrutinib (+/- obinutuzumab) therapy vs. pre-treated patients enrolled for later-line acalabrutinib therapy. ***Coding*** AEs will be graded according to the CTCAE, version 5.0. AEs will be coded using the medical dictionary for regulatory activities (MedDRA) version, respectively (for details refer to chapter 13.2). ***Final Analysis*** The database will be locked 2 months after end of study (EOS). The final analysis (FA) will be done 4 months after the database lock (DBL). The final study report (FSR) will be submitted 4 months after FA to the market authorization holder. Furthermore, one full publication will be submitted after the FA.
Planned Study Duration	30 months after first patient in (FPI) **Recruitment period:** 18 months **Treatment observation** Treatment will be observed and continuously documented for each patient during acalabrutinib administration until maximum (max.) 12 months after LPI, whatever comes first. **Follow-up** If end of acalabrutinib treatment is earlier than max. 12 months after LPI, patients will be followed for progression and survival status up to max. 12 months after LPI.

Observational Plan Summary (German)

Protokoll-Nummer des Sponsors	IOM-100473
Offizieller Titel	Eine nicht-interventionelle, prospektive, offene Beobachtungsstudie zur Bewertung der Wirksamkeit und Sicherheit von Acalabrutinib (Calquence®) bei Patienten mit chronischer lymphatischer Leukämie (CLL), die eine direkte orale Antikoagulation (DOAC) erhalten.
Kurztitel/ Akronym	Acalabrutinib bei Patienten mit chronischer lymphatischer Leukämie unter direkter oraler Antikoagulation (CICERO)
Sponsor der Studie	iOMEDICO
Wissenschaftlicher Leiter	[redacted]
Studiendesign	Dies ist eine prospektive, beobachtende, multizentrische, nicht-interventionelle Kohortenstudie bei behandlungsbedürftigen CLL-Patienten, unter Co-Medikation mit einem DOAC (d.h. Edoxaban, Rivaroxaban, Dabigatranetexilat und Apixaban) für eine andere Erkrankung. Die Durchführung dieser NIS nimmt keinen Einfluss auf die Entscheidungen des behandelnden Arztes hinsichtlich therapeutischer und diagnostischer Verfahren, der Häufigkeit der medizinischen Untersuchungen oder anderen Maßnahmen während und nach der Behandlung. Alle Daten werden im Rahmen der klinischen Routine erhoben.
Studienerkrankung / Bedingung / Indikation	Erwachsene Patienten (≥18 Jahre) mit zuvor unbehandelter oder behandelter CLL, die unter Co-Medikation mit einem DOAC sind, und Behandlungsentscheidung für Acalabrutinib (Calquence®).
Studienbehandlung / Studienaktivität	Acalabrutinib (Calquence®) +/- Obinutuzumab (Gazyvaro®), gemäß der aktuellen Fachinformation (FI).
Geplante Anzahl Patienten und Studienzentren	50 Patienten (ausgenommen *Screening Failures* und Patienten mit einem *Off-label use* oder die die Ein- und Ausschlusskriterien verletzen, was nach Beginn der Therapie detektiert wurde) 20 (hämatologische und/oder onkologische Einrichtungen (niedergelassene medizinische Hämatologen/Onkologen, hämatologische/onkologische Ambulanzen, (Universitäts-) Krankenhäuser) in Deutschland)
Studienrationale	Die chronische lymphatische Leukämie (CLL) ist die häufigste hämatologische Malignität in der westlichen Hemisphäre und macht fast 25% aller Leukämien aus. Das mittlere Alter zum Zeitpunkt der Diagnose liegt bei über 70 Jahren, wobei mehr als 70% der Patienten älter als 65 Jahre sind.[1,2] Ältere CLL-Patienten leiden häufig an mehreren kardiovaskulären Begleiterkrankungen wie Vorhofflimmern, tiefen Venenthrombosen oder Lungenembolien, die zu einer sekundären Prophylaxe mit einem Antikoagulanz führen können.[3] Darüber hinaus treten bei 80% der älteren Patienten ischämische Schlaganfälle auf, die ebenfalls mit Antikoagulanzien behandelt

	werden können.[4] Das Management von kardiovaskulären Komobiditäten sind eine große Herausforderung bei CLL-Patienten. Für die Antikoagulation stehen mehrere Medikamente zur Verfügung, darunter Vitamin-K-Antagonisten (VKA), unfraktioniertes Heparin und niedermolekulare Heparine. Seit kurzem sind neue direkte orale Antikoagulanzien (DOAC), d.h. Faktor-Xa-Inhibitoren (Edoxaban, Rivaroxaban, Apixaban) oder Thrombininhibitoren (z.B. Dabigatranetexilat) verfügbar und erweitern die Behandlungsmöglichkeiten. Bei Krebspatienten ist die Behandlung von venösen Thromboembolien (VTE) mit einem erhöhten Risiko von Blutungen verbunden und muss sorgfältig überwacht werden.[5] Die Rate schwerer Blutungsereignisse lag bei Krebspatienten, die mit Edoxaban behandelt wurden, bei 6,9 %, wie die HOKUSAI-Studie (NCT02073682) zeigte[6], wohingegen bei Nicht-Krebspatienten mit Vorhofflimmern, die Dabigatran erhielten, lag die Rate schwerer Blutungsereignisse bei etwa 3,7% lag.[7] Der klinische Verlauf der CLL ist heterogen. Die meisten Patienten sind asymptomatisch und benötigen keine aktive Therapie. Andere Patienten leiden jedoch unter einer Organbeteiligung, d.h. Lymphadenopathie und/oder Hepatosplenomegalie, oder unter B-Symptomen wie anhaltendem Fieber, Nachtschweiß und/oder ungewolltem Gewichtsverlust sowie Müdigkeit.[2] Die Indikation zur Behandlung basiert hauptsächlich auf den Symptomen, dem Blutbild und den Ergebnissen der körperlichen Untersuchung.[2] Das Ansprechen auf die Behandlung sollte gemäß den Leitlinien des International Workshop of CLL beurteilt werden.[22] Die Behandlung der CLL ist in der Regel nicht kurativ, aber die Patienten können Remissionen und eine langfristige Stabilisierung ihrer Krankheit erreichen. Bei den meisten Patienten kommt es jedoch zu einem Rückfall. Für die CLL stehen mehrere Behandlungsstrategien zur Verfügung, darunter konventionelle Chemotherapie in Kombination mit Anti-CD20 monoklonalen Antikörpern. Die Art der Behandlung, insbesondere bei der Erstbehandlung, richtet sich nach der klinischen Eignung und den genetischen Veränderungen (z.B. *TP53*) des CLL-Klons. Aktuelle Behandlungsrichtlinien empfehlen die Behandlung von neu diagnostizierter CLL bei Patienten im Binet-Stadium C und im Stadium B oder A mit zusätzlich erfüllten Kriterien (z.B., massive Splenomegalie oder Lymphadenopathie).[9] Für Patienten ohne *TP53*-Mutation oder komplexen Karyotyp wird ein Bruton-Kinase-Inhibitor (BTKi) als Monotherapie oder in Kombination mit einem Anti-CD20-Antikörper oder einer Chemotherapie (Fludarabin, Cyclophosphamid, Rituximab (FCR)-Schema) oder Venetoclax in Kombination mit Obinutuzumab als Erstbehandlung empfohlen. Für ältere und komorbide Patienten wird anstelle von FCR Bendamustin + Rituximab oder Chlorambucil + Obinutuzumab in der Erstlinie empfohlen. Für Patienten mit einer *TP53*-Mutation oder einem komplexen Karyotyp wird als Erstlinienbehandlung ein BTKi als Monotherapie oder in Kombination mit einem Anti-CD20-Antikörper oder Venetoclax in Kombination mit Obinutuzumab empfohlen. Als Zweitlinientherapie wird ein BTKi oder Venetoclax in Kombination mit Rituximab empfohlen, je nach Ansprechen auf die Erstlinientherapie und Krankheitsmerkmalen.[9] Darüber hinaus gibt es keine Standard-Kombinationstherapie für Patienten mit rezidivierter CLL. Daher besteht ein dringender medizinischer Bedarf, neue Strategien zu entwickeln.[1] BTKis wie Ibrutinib, Zanubrutinib oder Acalabrutinib haben in fast allen Untergruppen eine große Wirksamkeit gezeigt und sind daher für die Mehrheit der Patienten eine Standardbehandlung geworden, ungeachtet von Untergruppen wie Alter oder Risikogruppen.[10,11] Bei therapienaiven (TN) und rezidivierten/refraktären (R/R) CLL-Patienten wurde unter Ibrutinib eine Gesamtansprechrate (ORR) von 88% bzw. 87% erzielt.[10,12] Bei therapienaiven Patienten, die mit Zanubrutinib behandelt wurden, wurde in einer frühen klinischen Studie eine ORR von 94,5% erzielt.[13,14] Bei mit Acalabrutinib

	behandelten Patienten wurde eine ORR von 80% in R/R-CLL und 86% bis 95% in TN CLL Patienten erzielt.[11,15] Frühe klinische Studien haben ein höheres Blutungsrisiko bei Patienten mit BTKis gezeigt.[10,11,15] Bei Patienten, die mit Ibrutinib oder Zanubrutinib behandelt wurden, traten in ~48% Blutungen jeglichen Grades auf.[10,13] Bei Patienten, die mit Acalabrutinib-Monotherapie oder Kombinationstherapie behandelt wurden, war die Rate mit ~30% niedriger. Blutungen ≥3 Grades wurden bei 2-3% der mit Acalabrutinib behandelten Patienten festgestellt.[11,15] Bislang gibt es keine prospektiven Daten zu Wechselwirkungen zwischen BTKis und DOACs. In einer retrospektiven Kohortenstudie wurde das Risiko schwerer Blutungsereignisse bei 30 Patienten mit B-Zell-Lymphom untersucht, die mit Ibrutinib und DOACs behandelt wurden. Schwere Blutungsereignisse, definiert als Grad 3 oder 4, wurden bei 16,6% der Patienten identifiziert.[16] Dennoch ist die Mehrheit der Ärzte in Deutschland zurückhaltend bei der Verwendung von BTKis bei Patienten, die eine Komedikation mit DOACs erhalten, wodurch diesen Patienten eine wirksame und ansonsten sichere Behandlung vorenthalten wird und sie sich für andere, potenziell weniger verträgliche Behandlungsoptionen wie z.B. FCR entscheiden müssen. Ziel von CICERO ist die Untersuchung der klinischen Ergebnisse von Acalabrutinib (+/- Obinutuzumab) in CLL Patienten die unter Co-Medikation mit DOACs (Edoxaban, Rivaroxaban, Dabigatranetexilat, Apixaban) sind, mit besonderem Schwerpunkt auf prospektiven Daten zur Sicherheit unabhängig der Anzahl an Vortherapien.

Studienziele und Endpunkte	Ziel dieser NIS ist die Bewertung der Sicherheit mit dem Fokus auf Blutungsereignisse bei erwachsenen Patienten mit CLL, die Acalabrutinib und Co-Medikation mit einem DOAC, in der klinischen Routine.
	• Bewertung von Blutungsereignissen bei Patienten, die Acalabrutinib und eine gleichzeitige Behandlung mit DOAC erhalten
	  • Inzidenzanteil Patienten mit schwerwiegenden Blutungsereignissen nach Schulman et al.[17] (Primärer Endpunkt)
	  • Inzidenzanteil Patienten mit klinisch relevantem nicht-schwerwiegendem (CRNM) Blutungsereignis (Haupt-Sekundärer Endpunkt)[21]
	  • Inzidenzanteil Patienten mit schweren (nach Schulman et al.) und/oder CRNM Blutungsereignissen (Haupt-Sekundärer Endpunkt)
	  • Inzidenzanteil Patienten mit schweren Blutungen nach Ghia et al.[15] (Haupt-Sekundärer Endpunkt)
	  • Inzidenzanteil Patienten mit Blutungsereignissen jeglicher Art und Schwere (Sekundärer Endpunkt)
	  • Zeit bis zum ersten Auftreten von schweren Blutungen nach Schulman et al. (Sekundärer Endpunkt)
	  • Inzidenzanteil Patienten mit Blutungen im zentralen Nervensystem (ZNS-Blutungen) (Sekundärer Endpunkt)
	• Bewertung der Sicherheit bei Patienten, die Acalabrutinib und eine gleichzeitige Behandlung mit DOAC erhalten (Sekundäres Studienziel)
	  • Sterblichkeit (jeder Ursache) unter Acalabrutinib-Therapie
	• Bewertung der Sicherheit bei Patienten, die Acalabrutinib und eine gleichzeitige Behandlung mit DOAC erhalten, hinsichtlich der Wechselwirkungen mit der Wirksamkeit des DOACs (Sekundäres Studienziel)
	  • Inzidenzanteil Patienten mit VTE-bedingter Todesursache

	• Inzidenzanteil Patienten mit erstmals aufgetretenem oder wiederkehrendem ischämischem Schlaganfall oder systemischer arterieller Embolie oder venösem thromboembolischem Ereignis • Bewertung der Wirksamkeit von Acalabrutinib bei Patienten, die mit einem DOAC behandelt werden (Sekundäres Studienziel) • Gesamtansprechrate (ORR) • Progressionsfreies Überleben (PFS) • Gesamtüberleben (OS) • Bewertung der Parameter für die Therapieentscheidung mit Acalabrutinib (Sekundäres Studienziel) • Parameter, die die Wahl der Therapie beeinflussen • Detaillierte Beschreibung der Behandlung (Sekundäres Studienziel) • Einzelheiten zu früheren Therapien • Einzelheiten der Acalabrutinib-Behandlung mit oder ohne Obinutuzumab und der Behandlung mit DOAC • Häufigkeit der begleitenden Medikation außer DOAC
Einschlusskriterien	Die Patienten müssen alle folgenden Kriterien erfüllen, um in die Studie aufgenommen zu werden: • 18 Jahre alt oder älter • Patienten mit Chronisch Lymphatischer Leukämie (CLL) und der Entscheidung für eine Behandlung mit Acalabrutinib (+/- Obinutuzumab) gemäß der aktuellen FI nach Einschätzung des behandelnden Arztes oder bereits begonnene Behandlung mit Acalabrutinib (+/- Obinutuzumab) nicht länger als 6 Wochen zuvor. • Andere Erkrankungen und daraus resultierende medizinische Notwendigkeit einer direkten oralen Behandlung mit Antikoagulanzien oder bereits unter Behandlung mit Antikoagulanzien wie Edoxaban (Lixiana®) oder Rivaroxaban (Xarelto®) oder Dabigatranetexilat (Pradaxa®) oder Apixaban (Eliquis®) gemäß der aktuellen FI. • ECOG 0-2 • Unterzeichnete, schriftliche Einverständniserklärung.
Ausschlusskriterien	Der Patient ist nicht teilnahmeberechtigt, wenn eines der folgenden Kriterien erfüllt ist: • Kombination von Acalabrutinib mit anderen Substanzen als Obinutuzumab zur Behandlung der CLL • Teilnahme an einer interventionellen klinischen Studie mit Acalabrutinib.
Erfassung der Wirksamkeit	Das Ansprechen der CLL und der Lymphknoten und/oder potenziell befallenen Organe (z.B. Leber, Milz) wird nach lokalen medizinischen Standards, die gemäß den Leitlinien empfohlen werden, vom Beginn der Behandlung mit Acalabrutinib bis zur Progression (PD) der CLL oder zum Tod, je nachdem, was zuerst eintritt, beurteilt und bewertet. Das Fortschreiten der Erkrankung und das Überleben werden 12 Monate lang nach der Aufnahme des letzten Patienten (LPI) verfolgt.

Erfassung der Sicherheit und Verträglichkeit	Gemäß der klinischen Routine • Kontinuierliche Erfassung und Einstufung aller unerwünschten Ereignisse (UEs) einschließlich schwerwiegender unerwünschter Ereignisse (SUEs) gemäß NCI CTCAE v 5.0. nach Unterschrift der Einwilligungserklärung der NIS, während der Behandlung mit Acalabrutinib und den folgenden 30 Tagen nach Ende der Acalabrutinib Behandlung. (Weder von Patienten gemeldete Symptome noch Fragebögen werden auf versteckte unerwünschte Ereignisse überprüft). Bei retrospektiv eingeschlossenen Patienten sind zusätzlich alle in den Krankenakten dokumentierten (S)AEs zu melden, die von Beginn der Therapie bis zur Aufnahme in die Studie aufgetreten sind. • Überwachung von Laborwerten (einschließlich Tests zur Gerinnungsüberwachung und Thrombozytenzahl/Funktionstests, sofern diese in der klinischen Routinepraxis des dokumentierenden Studienzentrums durchgeführt werden)
Erfassung der ‚patient-reported outcomes' (PROs)	Die Teilnahme der Patienten am PRO-Modul ist erforderlich • Patientenfragebogen zu Blutungsereignissen in Anlehnung an das *Bleeding Assessment Tool* der *International Society on Thrombosis and Hemostasis*.[18–20] Der Fragebogen wird vom Studienzentrum an die Patienten bei jedem Besuch des Patienten in der Praxis verteilt während der Behandlung mit Acalabrutinib. Für Patienten, die retrospektiv eingeschlossen wurden, wird der Fragebogen zusätzlich bei Einschluss ausgegeben. Die Patienten werden gefragt, ob in der Zeit zwischen dem letzten Besuch und dem aktuellen Besuch bestimmte Ereignisse aufgetreten sind (oder zwischen Start der Therapie und dem Einschluss für retrospektiv eingeschlossene Patienten bei Einschluss), und besprechen den Fragebogen mit dem Arzt, um festzustellen, ob ein UE aufgetreten ist. Dieser Fragebogen wird nur als Dokumentationshilfe verwendet und wird nicht in den eCRF übertragen, sondern gilt als Quelldokument. Das Aushändigen sowie das Ausfüll-Datum werden im eCRF dokumentiert.
Weitere Erfassungen	• Angaben zu früheren Behandlungen (einschließlich Transplantationen, Strahlentherapien und antineoplastische Behandlungen) (Beginn/Enddaten / Substanzen / Transplantationstyp / Mobilisierung / Hochdosistherapie / PD mit Datum des PD / Gründe für das Ende der Behandlung) • Einzelheiten zur Acalabrutinib-Behandlung (einschließlich Beginn/Enddatum, Dosis, Dosisänderungen mit Gründen, Gründe für das Ende der Behandlung) • Angaben zur Behandlung mit Obinutuzumab (einschließlich Beginn/Enddatum, Gründe für das Ende der Behandlung) • Angaben zur DOAC-Behandlung (einschließlich Art des DOACs Beginn/Enddatum, Dosis, Dosisänderungen mit Gründen, Grund für die Behandlung, Gründe für die Beendigung der Behandlung) • Einzelheiten zu Operationen oder Strahlentherapien während der Acalabrutinib-Behandlung (z.B. Datum des Auftretens / Beginn / Ende der Behandlung, Indikation) • Behandlungsentscheidung des Arztes zu Beginn der Behandlung anhand eines Fragebogens mit verschiedenen Faktoren, die möglicherweise die Behandlungsentscheidung beeinflussen, wie z. B. Alter, Komorbiditäten, Leitlinien. • Begleitmedikation (Substanz, Anfangs-/Enddatum, Grund für die Anwendung) mit Schwerpunkt auf Arzneimitteln zur Behandlung von Anämie,

	Thrombozytopenie, Durchfall, Erbrechen, Infektionen sowie anderen Gerinnungshemmern als DOAC
Statistik und Datenanalyse	*Fallzahl* Aufgrund des explorativen Charakters der Studie wird keine formale Fallzahlberechnung durchgeführt, da keine Hypothesentestung erfolgt. Es werden N=50 Patienten in die Studie aufgenommen. Für den primären Endpunkt, die Rate schwerer Blutungen, kann mit dieser Fallzahl folgende Genauigkeit (95% Konfidenzintervall) erreicht werden in Abhängigkeit der beobachteten Events: **Fallzahl** | **Anteil Patienten mit schweren Blutungen** | **95% Konfidenzintervall (exact Clopper-Pearson)** 50 | 2% | 0,05% - 10,65% 50 | 3% | 0,22% - 12,22% 50 | 4% | 0,49% -13,71% 50 | 5% | 0,84% - 15,15% *Analysen zur Sicherheit* *Anteil Patienten mit schweren Blutungen nach Schulman et al. (Häufigkeiten):* Eine Blutung wird als schwer definiert, wenn sie tödlich ist und/oder symptomatisch an einer kritischen Stelle auftritt (wie z.B. intrakraniell, intraspinal, intraokular, retroperitoneal, intraartikulär oder perikardial oder intramuskulär mit Kompartmentsyndrom)und oder mit einem Hämoglobinabfall von 2 g/dl (1,24 mmol/l) oder mehr einhergeht oder eine Transfusion von 2 oder mehr Bluteinheiten erfordert.[17] *Anteil Patienten mit klinisch relevanten nicht-schweren (CRNM) Blutungen (Häufigkeiten):* Klinisch relevante nicht-schwere Blutungen (CRNM-Blutungen) sind definiert als Blutungen, die nicht die Kriterien für schwere Blutungen nach Schulman et al. erfüllen, aber mit der Notwendigkeit eines medizinischen Eingriffs, des Kontakts mit einem Arzt oder Hospitalisierung oder Intensivierung der Versorgung einhergeht.[21] *Anteil Patienten mit schweren Blutungen nach Ghia et al. (Häufigkeiten):* Als schwere Blutungen gelten alle schweren Blutungen oder Blutungen des Grades ≥3 oder ZNS-Blutungen jeglichen Grades, ausgenommen immunthrombozytopenische Purpura.[15] *Anteil Patienten mit schweren (nach Schulman et al.) und/oder CRNM Blutungen (Häufigkeiten):* Es wird die Häufigkeit von Patienten mit schweren oder CRNM Blutungen angegeben. *Anteil Patienten mit (irgend)einem Blutungsereignis jeder Art (Häufigkeiten)* *Zeit bis zum ersten Auftreten von schweren Blutungen:* Es wird eine Competing Risk Analyse (konkurrierendes Ereignis: Tod) durchgeführt. *Anteil Patienten mit ZNS-Blutungen (Häufigkeiten)*

	Sterblichkeit aus allen Gründen: Anteil Patienten, die während der Acalabrutinib-Therapie oder innerhalb von 30 Tagen nach der letzten Dosis verstorben sind. *Anteil Patienten mit VTE-bedingter Todesursache (Häufigkeiten)* *Anteil Patienten mit neuem oder wiederkehrendem ischämischem Schlaganfall oder systemischer arterieller Embolie oder venösem thromboembolischem Ereignis (Häufigkeiten).* *Wirksamkeitsanalysen* *ORR (Häufigkeiten):* ist definiert als der Anteil der Patienten, die insgesamt auf die Behandlung ansprechen (CR/PR). *PFS:* ist definiert als die Zeit vom Beginn der Acalabrutinib-Therapie bis zum ersten Auftreten einer progressiven Erkrankung oder zum Tod, je nachdem, was zuerst eintritt. Es wird nach der Kaplan-Meier-Methode ausgewertet. *OS:* ist definiert als die Zeit vom Beginn der Acalabrutinib-Behandlung bis zum Tod. Es wird mit der Kaplan-Meier-Methode analysiert. *Therapieentscheidung* *Parameter der Therapieentscheidung:* Die Häufigkeit der einzelnen Parameter, die die Therapieentscheidung beeinflussen, wird angegeben. *Angaben zur Behandlung* *Häufigkeit früherer Therapien* *Angaben zur Behandlung mit Acalabrutinib und DOAC (Häufigkeiten, deskriptive Statistiken)*. *Häufigkeit der begleitenden Medikation außer DOAC:* Anti-Anämie-, Anti-Thrombozytopenie-, Antikoagulations-, Antiemetika-, Anti-Durchfall-, Anti-Infektions- und Anti-Hyperurikämie-Medikamente. *Subgruppen* Wirksamkeitsparameter (ORR, PFS, OS) werden in der Subgruppe der Patienten, die zur Erstlinienbehandlung mit Acalabrutinib (±Obinutuzumab) eingeschlossen wurden gegenüber vorbehandelten Patienten, die mit einer Acalabrutinib-Therapie in einer höheren Linie eingeschlossen wurden, analysiert. *Coding* UEs werden nach den CTCAE, Version 5.0, eingestuft. Für die Kodierung der unerwünschten Ereignisse wird MedDRA verwendet (Details siehe Kapitel 13.2). *Finale Analyse*

	Die Datenbank wird 2 Monate nach EOS gesperrt. Die finale Analyse (FA) wird 4 Monate nach Datenbankschluss (Data base lock (DBL)) durchgeführt. Der finale Studienreport (FSR) wird 4 Monate nach der FA beim Arzneimittelhersteller eingereicht. Außerdem wird nach der FA eine Publikation eingereicht.
Geplante Studiendauer	30 Monate nach Einschluss des ersten Patienten (*first patient in* (FPI)) **Rekrutierungszeitraum:** 18 Monate **Beobachtung der Behandlung:** Die Behandlung wird für jeden Patienten während der Verabreichung von Acalabrutinib maximal (max.) bis 12 Monate nach dem Einschluss des letzten Patienten in die Studie (*last patient in* (LPI)) beobachtet und kontinuierlich dokumentiert, je nachdem, was zuerst eintritt. **Follow-up** Sollte die Acalabrutinib-Behandlung vor max. 12 Monate nach LPI beendet werden, werden die Patienten bis max. 12 Monate nach dem LPI auf ihren Progress und Überlebensstatus hin beobachtet.

List of Abbreviations and Glossary of Terms

(S)UE	*(Schwerwiegendes) unerwünschtes Ereignis*
µl	Microliter
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial fibrillation
AKT	Protein kinase B
ALT	Alanine transaminase
AMG	*Arzneimittelgesetz*
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATM	Ataxia Telangiectasia mutated
BCR	B cell receptor
BTK	Bruton tyrosine kinase
BTKi	Bruton t*yrosine* kinase inhibitor
bzw.	*beziehungsweise*
CCI	Charlson Comorbidity Index
CD	Cluster of differentiation
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete Response
CRNM	Clinically relevant non-major bleeding
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
d.h.	*das heißt*
DBL	Database Lock
del	deletion
dl	Deciliter
DOAC	Direct oral anticoagulation
DOR	Duration of Response
DVT	Deep vein thrombosis
e.g.	*Exempli gratia*
ECOG	Eastern Cooperative Oncology Group

eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
EOS	End of Study
ERK	Extracellular-signal regulated kinase
FA	Final Analysis
FAS	Full Analysis Set
FCR	Fludarabine, Cyclophosphamide, Rituximab
FI	*Fachinformation*
FPI	First Patient In
FSR	Final Study Report
FU	Follow-up
g	Gram
Gamma-GT	Gamma-glutamyltransferase
GFR	Glomerular filtration rate
GOT	Glutamic oxaloacetic transaminase
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GPT	Glutamic pyruvate transaminase
GVP	Good Pharmacovigilance Practices (Guidelines for)
HR	Hazard Ratio
i.e.	*Id est*
ICF	Informed Consent Form
ID	Identity
IGHV	Immunoglobulin heavy chain variable region
IKZF3	IKAROS family zinc finger 3
INR	International Normalized Ratio
IPI	International prognostic Index
ISTH - BAT	International Society on Thrombosis and Hemostasis – Bleeding Assessment Tool
ITK	Interleukin-2-inducible T-cell kinase
iwCLL	International Workshop of CLL
IκB	Inhibitor of nuclear factor B
l	Liter
LPI	Last Patient In
LPO	Last Patient Out
MAH	Marketing authorization holder

max.	maximum
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedRA	Medical Dictionary for regulatory activities
mg	Microgram
min	Minutes
mmol/l	Millimole per liter
MPV	Mean platelet volume
MRD	Minimal Residual Disease
MRI	Magnet Resonance Imaging
NA	Not applicable
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NIS	Non-Interventional Study / *Nicht-interventionelle Studie*
NR	N*ot reached*
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Pulmonary embolism
PFS	Progression-free Survival
PI3K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
PLCγ2	Phospholipase Cγ2
PR	Partial Response
PRO	Patient-Reported Outcome
PTT	Partial thromboplastin time
R/R	Relapsed/refractory (relapsed or refractory)
RDW	Red blood cell distribution width
SAE	Serious Adverse Event
SD	Stable disease
SF3B1	Splicing factor 3b subunit 1
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
ß2MG	Beta-2 microglobulin

TCT	Thrombin clotting time
TEAE	Treatment-emergent Adverse Event
TN	Treatment-naïve
TP53	Tumor proto-oncogene 53
TT	Thrombin time
UE	*Unerwünschtes Ereignis*
VKA	Vitamin K antagonist / *Vitamin-K-Antagonist*
vs.	versus
VTE	Venous thromboembolism
WBC	White blood count
z.B.	*Zum Beispiel*
ZNS	*Zentrales Nervensystem*

Table of Contents

1. Introduction

1.1. Chronic lymphocytic leukemia (CLL)

1.1.1. Incidence and epidemiology

Chronic lymphocytic leukemia (CLL) is the most common hematological malignancy in the western hemisphere, accounting for nearly 25% of all leukemias. The median age at time of diagnosis is >70 years, with more than 70% of patients being older than 65 years.[1,2]

Clonal proliferation and accumulation of B cells within blood, bone marrow, lymph nodes and spleen are characteristic for CLL.[23]. Chromosomal aberrations are mainly found as the initiating aberration of the disease which are later followed by additional mutations. Deletions, i.e., (del)(13q), del(11q), trisomy 12 and del(17p) are among the most important cytogenetic aberrations. Recurrently mutated genes in CLL patients are *immunoglobulin heavy chain variable region* (*IGHV*), *myeloid differentiation primary response 88* (*MYD88), tumor proto-oncogene 53 (TP53), ataxia telangiectasia mutated (ATM), IKAROS family zinc finger 3 (IKZF3),* and *splicing factor 3b subunit 1 (SF3B1)*.[23]

1.1.2. Symptoms, clinical manifestation and diagnosis

The clinical course of CLL is heterogenous. Most patients are asymptomatic. However, other patients suffer from organ involvement, i.e. lymphadenopathy and/or hepatosplenomegaly or B symptoms like persistent fever, night sweats and/or unintentional weight loss as well as fatigue.[2] The diagnosis of CLL is mostly established by blood counts, differential counts, blood smears and immunophenotyping. The presence of ≥5000 B-lymphocytes/µl in the peripheral blood for at least 3 months is required for the diagnosis of CLL. The clonality needs to be confirmed via flow cytometry. Typically expressed surface antigens are CD5, CD19, CD20 and CD23.[23]

Not all patient with CLL require treatment. Indication for treatment is mainly based on symptoms, complete blood cell count and physical examination.[2]

1.1.3. Staging, prognostic factors, risk stratification and therapeutic options

The widely accepted clinical staging for CLL are Rai (Table 1) and Binet (Table 2).[23–25] Both systems describe three major groups and are simple and inexpensive.

Table 1. Staging according to Rai.[25]

Stage	Definition
0 – low-risk	Lymphocytosis (>30% lymphoid cells) in peripheral blood and/or bone marrow only
I – intermediate-risk	Lymphocytosis (>30% lymphoid cells) and lymphadenopathy
II – intermediate-risk	Lymphocytosis, Lymphadenopathy +/- hepato/splenomegaly
III – high-risk	Lymphocytosis + anemia (<11 g/dl) with or without lymphadenopathy and/or organomegaly
IV – high risk	Lymphocytosis and thrombocytopenia (<100 x 10^9/l) with or without lymphadenopathy, organomegaly, and/or anemia

Table 2. Staging according to Binet.[24]

Stage	Definition
A	• Hemoglobin ≥10 g/dl • Thrombocytes ≥100,000/µl • <3 involved regions (lymph nodes (axillary, cervically, inguinale), liver or spleen)
B	• Hemoglobin ≥10 g/dl • Thrombocytes ≥100,000/µl • ≥3 involved regions (lymph nodes (axillary, cervically, inguinale), liver or spleen)
C	• Hemoglobin <10 g/dl • Thrombocytes <100,000/µl

The currently most relevant prognostic score including also other parameters, like biomarkers, is the CLL International prognostic Index (CLL-IPI) (Table 3). This prognostic index uses five independent prognostic factors: *TP53* deletion and/or mutation, *IGHV* mutation, serum beta-2 (ß2)-microglobulin (ß2MG), clinical stage and age.[23,26]

Table 3. The CLL-IPI.[26]

Prognostic factor		**Points**
TP53 deletion and/or mutation		4
Unmutated *IGHV* genes		3
Serum ß2-microglobulin >3.5 mg/l		2
Rai stage I-IV or Binet B-C		1
Age >65 years		1
Cumulative CLL-IPI score	**Risk category**	**5-year treatment free survival**
0-1	Low risk	78%
2-3	Intermediate risk	54%
4-6	High risk	32%
7-10	Very high risk	0%

Treatment of CLL is usually not curative, but patients can achieve remissions and long-term stabilization of their disease. However, most patients eventually relapse. Several treatment strategies are available for CLL including conventional chemotherapy protocols combined with anti-CD20 monoclonal antibodies. Type of treatment, especially in first line, is based on clinical fitness and genetic alterations (e.g., *TP53*) of the CLL clone.

Response to treatment should be assess according to the International Workshop of CLL (iwCLL) guidelines.[8,22] Diagnostic tests which are always recommend include physical examination and blood and/or bone marrow tests. The following response categories can be defined: complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) (Table 4). If available, also the measurement if minimal residual disease (MRD) can be included.[8]

Table 4. Response criteria according to the iwCLL guidelines[8].

Parameter	**CR**	**PR**	**SD**	**PD**
Lymph nodes	None ≥1.5 cm	Decrease ≥50% from baseline	Change of -49% to +49%	Increase ≥50% (from baseline or response)
Liver and/or spleen size	Spleen size <13 cm; liver size normal	Decrease ≥50% from baseline	Change of -49% to +49%	Increase ≥50% (from baseline or response)
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Change of -49% to +49%	Increase ≥50% (over baseline)
Platelet count	≥100x10^9/l	≥100x10^9/l or increase ≥50% over baseline	Change of -49% to +49%	Decrease ≥50% (from baseline secondary to CLL)
Hemoglobin	≥11 g/dl (un-transfused and without erythropoietin)	≥11 g/dl or increase ≥50% over baseline	Increase <11.0 g/dl or <50% over baseline, or decrease <2 g/dl	Decrease ≥2 g/dl (from baseline secondary to CLL)
Bone Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules or not done	No change in bone marrow infiltration	Increase of CLL cells by ≥50% on successive biopsy

In some patients, CLL can transform into a fast-growing, highly aggressive and treatment-refractory non-Hodgkin lymphoma (NHL) with a bad prognosis.[27]

Current treatment guidelines recommend treatment of newly diagnosed CLL in patients with Binet stage C and stage B or A with additional fulfilled criteria (e.g., massive splenomegaly or lymphadenopathy).[9] For patients with no *TP53* mutation or complex karyotype, a Bruton kinase inhibitor (BTKi) like ibrutinib or acalabrutinib as monotherapy or in combination with an anti-CD20 antibody or chemotherapy (fludarabine, cyclophosphamide, rituximab (FCR) regimen) or venetoclax in combination with obinutuzumab is recommended as first-line treatment.

For elderly and comorbid patients instead of FCR, bendamustine + rituximab or chlorambucil + obinutuzumab is recommend in the first line. For patients with a *TP53* mutation or complex karyotype, no chemotherapy, but a BTKi as monotherapy or in combination with an anti-CD20 antibody or venetoclax in combination with obinutuzumab is the recommended first-line treatment. As second-line therapy, a BTKi or venetoclax in combination with rituximab is recommended, depending on the response to first-line treatment and disease characteristics.[9] In addition, there is no standard combination therapy for patients with relapsed CLL. Therefore, there is an urgent medical need to identify new strategies.[1]

BTKis as ibrutinib, zanubrutinib or acalabrutinib have shown great efficacy in nearly all subgroups and have therefore become kind of a standard treatment for the majority of patients, despite subgroups as age or risk groups.[10,11] Treatment-naïve (TN) and relapsed/refractory (R/R) CLL patients showed an overall response rate (ORR) of 88% and 87%, respectively, when treated with ibrutinib.[10,12] TN patients treated with zanubrutinib showed an ORR of 94.5% in an early clinical study.[13,14]

1.2. Acalabrutinib (Calquence®)

1.2.1. Mechanism of action

Acalabrutinib (also known as ACP-196 and/or Calquence®) is a selective, irreversible small molecule inhibitor of BKT currently under clinical investigation. Acalabrutinib is an investigational product. Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, CLL, and small lymphocytic lymphoma (SLL).[23] It is a BTKi of the second generation, which is administered orally.[28] Acalabrutinib covalently binds to cysteine 481 of BTK and thus inhibits the phosphorylation of downstream targets like extracellular-signal regulated kinases (ERK), inhibitor of nuclear factor kappa B (IκB) through phospholipase Cγ2 (PLCγ2) and protein kinase C (PKC) and inhibits the protein kinase B (AKT) through phosphatidylinositol 3-kinase (PI3K). BTK is part of the B cell receptor (BCR) signaling pathway (Figure 1). Furthermore, it demonstrated higher selectivity for BTK compared to other kinases with a cysteine residue at the same position. Compared to ibrutinib, acalabrutinib does not inhibit epidermal growth factor receptor (EGFR), interleukin-2-inducible T-cell kinase (ITK) or TEC protein kinase.[29]

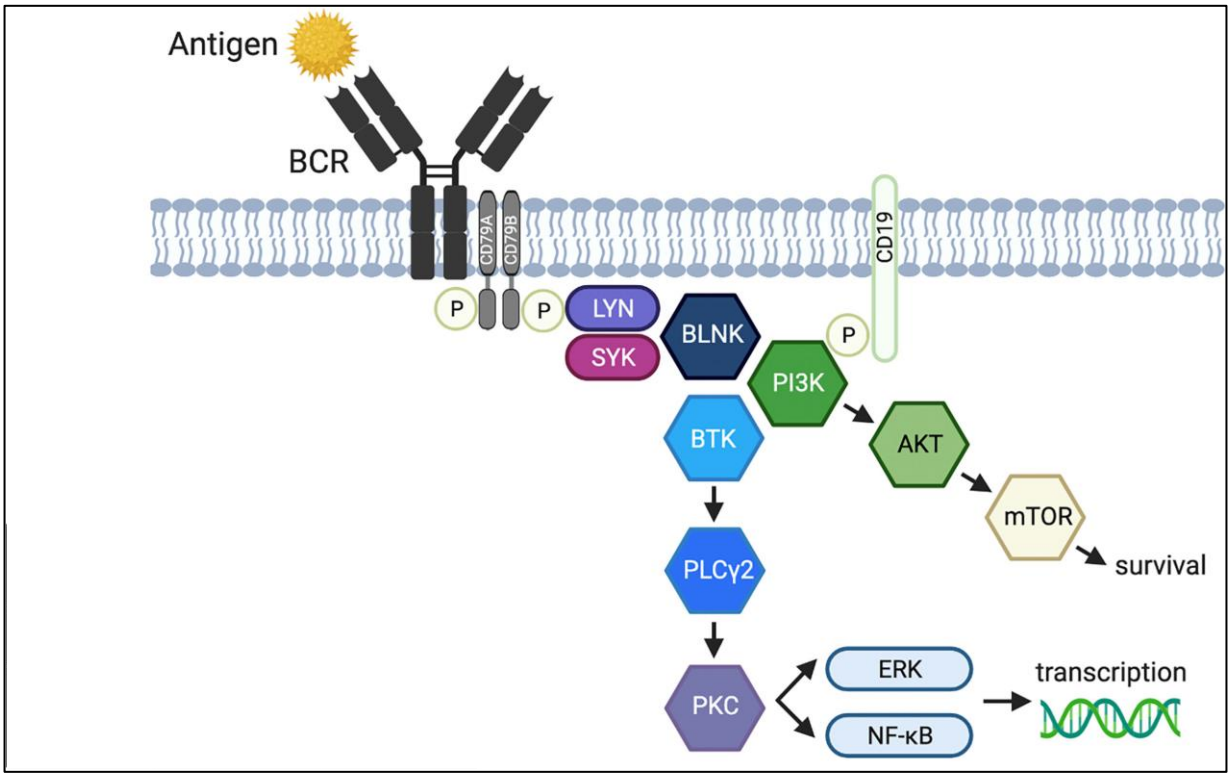

Figure 1. B cell receptor pachtway.[30]

1.2.2. Pivotal studies

Acalabrutinib was assessed in patient with TN and R/R CLL.

The ELEVATE-TN (NCT02475681) study was a multicenter, international, randomized phase 3 trial in TN CLL patients comparing acalabrutinib in combination with obinutuzumab versus (vs.) acalabrutinib alone vs. chlorambucil in combination with obinutuzumab. The primary endpoint was progression-free survival (PFS) in the chlorambucil with obinutuzumab arm compared to the acalabrutinib with obinutuzumab arm. In total, 535 patients were 1:1:1 randomized. 179 patients received acalabrutinib + obinutuzumab, 179 patients received acalabrutinib monotherapy and 177 patients received obinutuzumab + chlorambucil. After a median follow-up (FU) of 28.3 months median PFS was not reached (NR) for acalabrutinib + obinutuzumab vs. 22.6 months (95% confidence interval (CI) 20.2-27.6, hazard ratio (HR) 0.10, 95% CI 0.06-0.17; p<0.0001) in the obinutuzumab + chlorambucil cohort. Median PFS for acalabrutinib alone was also NR vs. 22.6 months (95% CI 20.2-27.6, HR 0.2, 95% CI 0.13-0.30; p<0.0001) in the obinutuzumab + chlorambucil group (Figure 2).[11]

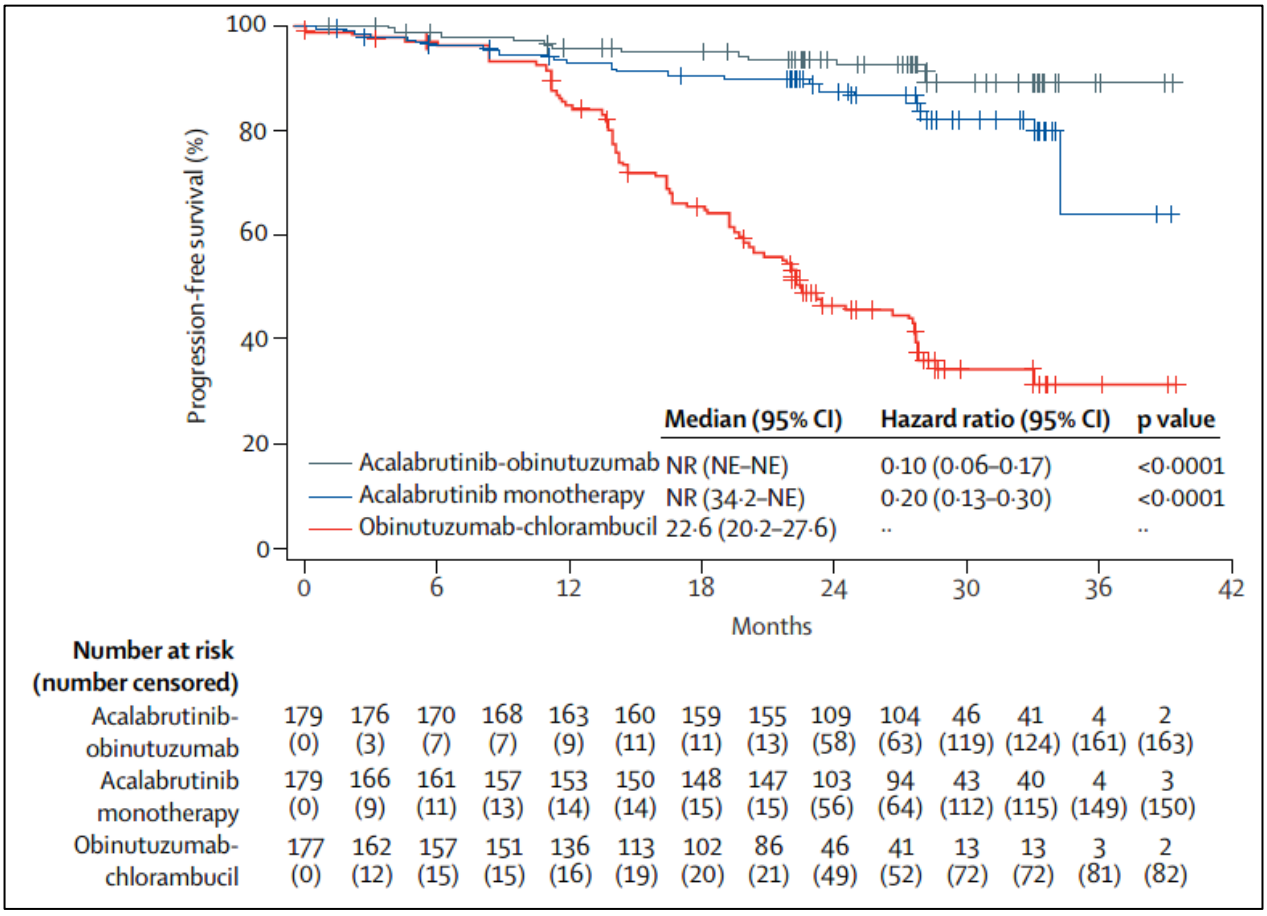

Figure 2. Progression-free survival (PFS) of treatment-naïve CLL patient in the ELEVATE-TN trial.[11]

The estimated 24-month PFS rate was 93% in the acalabrutinib + obinutuzumab group (95% CI, 87-96%) and 87% in the acalabrutinib monotherapy group (95% CI 81-92%) vs. 47% in the obinutuzumab + chlorambucil group (95% CI 39-55%). In all analyzed subgroups (e.g., patients with and without *IGHV* mutation, patient with del(11q22.3), patients with *TP53* mutations, patients with bulky disease) the acalabrutinib treatment with or without obinutuzumab was favored. At the data cutoff 24 months after last patient in (LPI), 79% of patients were still under treatment in each of the acalabrutinib groups. The best overall response was significantly better in the acalabrutinib + obinutuzumab (94%, 95% CI 98-97%) vs. the obinutuzumab + chlorambucil (79%, 95% CI 72-84%, p<0.0001) group. In the acalabrutinib monotherapy group, the overall response was 86% (95% CI 80-90%) which was also significantly better than in the chlorambucil group (p=0.089). In 24 patients (13%) in the acalabrutinib +

obinutuzumab group a CR was reached compared to 8 patients (5%) in the chlorambucil group. One patient (1%) achieved a CR in the acalabrutinib monotherapy group Figure 3).[11]

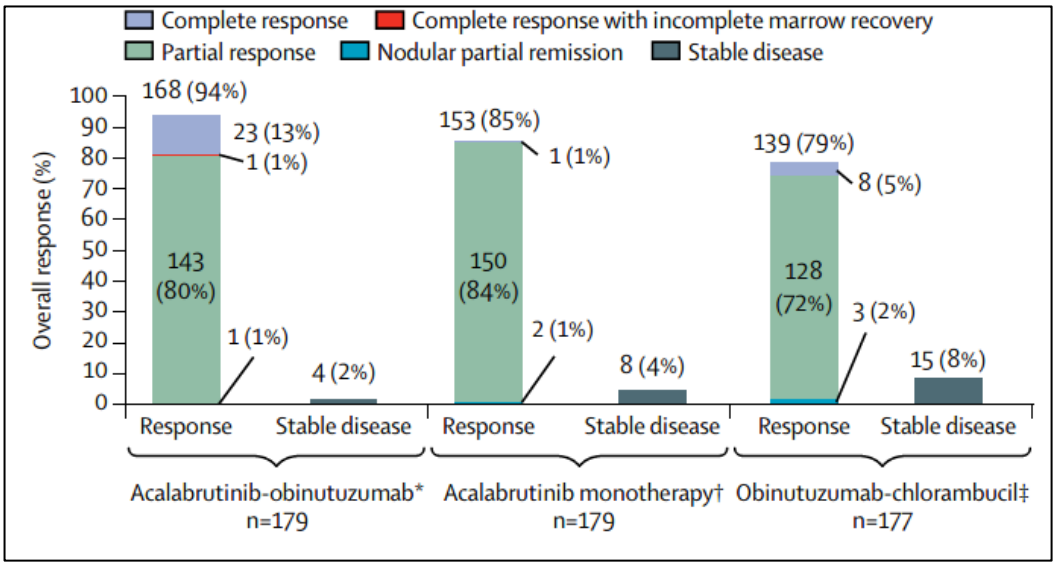

Figure 3. Best overall response.[11]

The median overall survival (OS) was NR in any group. Median time to next treatment was NR in any group. Progression with Richter's transformation occurred in one (1%) patient in the acalabrutinib + obinutuzumab group, five (3%) patients in the acalabrutinib monotherapy and one (1%) patient in the chlorambucil group.[11]

The ASCEND (NCT02970318) study was a multicenter, international, randomized phase 3 trial in R/R CLL patients comparing acalabrutinib monotherapy vs. investigator's choice (idelalisib + rituximab [I-R] or bendamustine + rituximab [B-R]). The primary endpoint was PFS assessed by an independent review committee in the intent-to-treat population. In total, 310 patients were 1:1 randomized. 155 patients received acalabrutinib monotherapy and 155 investigators choice (n=199 I-R, n=36 B-R). After a median FU of 16.1 months median PFS was NR for acalabrutinib vs. 16.5 months (95% CI 14.0-17.1, HR 0.31, 95% CI 0.20-0.49; p<0.0001) with investigator's choice (Figure 2). Median PFS was 15.8 and 16.9 months for patients receiving I-R and B-R, respectively. [15]

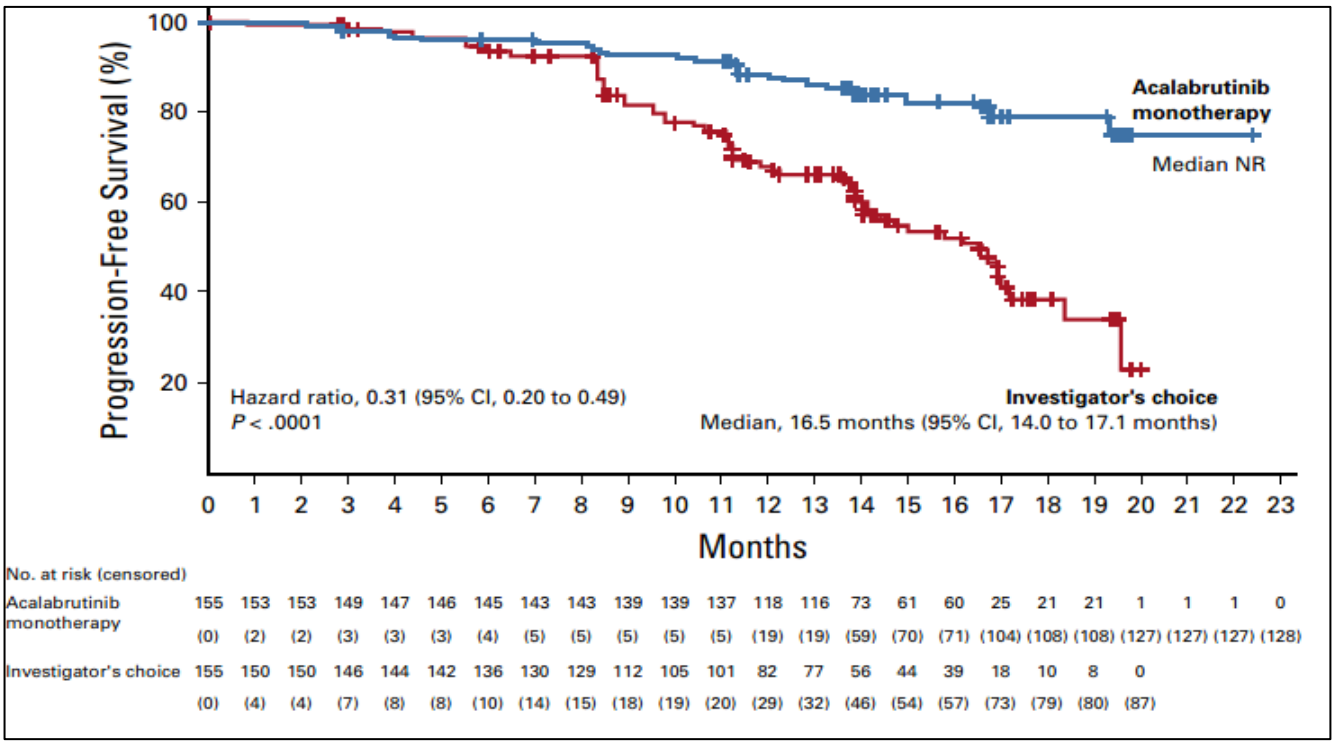

Figure 4. PFS in R/R CLL patients from the ASCEND trial.[15]

The estimated 12-month PFS rate was 88% (95% CI 81-92%) in the acalabrutinib group vs. 68% (95% CI 58-76%) and 69% (95% CI 50-82%) with I-R and B-R, respectively. In all prespecified subgroup analyses (e.g., patients with high-risk genomic features, such as del(17p), *TP53* mutation, del(11q) or unmutated *IGHV*) acalabrutinib monotherapy treatment also resulted in improved median PFS. ORR was similar with acalabrutinib monotherapy (81%) and investigator's choice (75%) (Figure 5). Median duration of response (DOR) was NR with acalabrutinib monotherapy and 13.6 months (95% CI 11.9 - NR) with investigator's choice (HR, 0.33; 95% CI, 0.19-0.59; p<0.0001).[15]

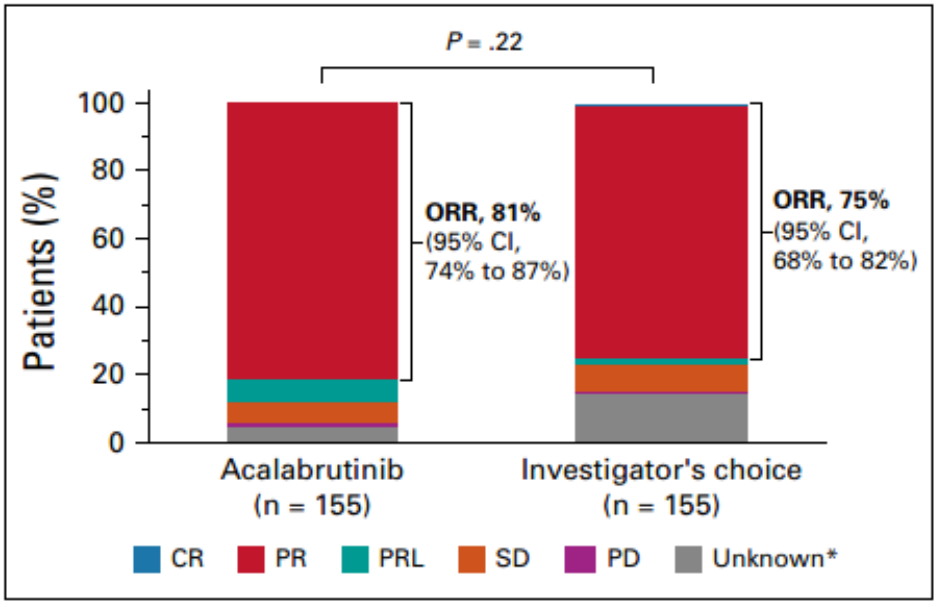

Figure 5. Overall response rate.[15]

The median OS was NR in any group. The 12-month OS rate was 94% for the acalabrutinib and 91% for the investigator's choice group. Median time to next treatment was NR in any group. At 12 months after LPI, 89% of

patients were still under treatment in the acalabrutinib group and 80% in the investigator's choice group. Progression with Richter's transformation occurred in four patients in the acalabrutinib group and five patients in the investigator's choice group (I-R n=4, B-R n=1).[15]

The ELEVATE-RR trial (NCT02477696) is a multicenter, randomized phase III trial evaluating acalabrutinib vs ibrutinib in pre-treated high-risk CLL patients. In total, 533 patients were randomized into the acalabrutinib arm (n=268) or ibrutinib arm (n=265). The trial was powered to show a non-inferiority to ibrutinib in terms of PFS. At a median follow-up of 40.9 months the median PFS was 38.4 month in both arms (HR 1.00; 95% CI 0.79–1.27). Median OS was not reached in either arm (HR 0.82 [95% CI 0.59–1.15]). Regarding occurrence of atrial fibrillation, acalabrutinib was statistically superior compared to ibrutinib (9.4% vs 16.0%; *P*=0.023). Also, in any-grade events of clinical interest like, cardiac, hypertension, and bleeding events were less frequent with acalabrutinib.[31]

1.2.3. Complementary studies

Not applicable

1.2.4. Safety profile and risk management measures

The most commonly observed adverse events (AEs) (any grade) in the pivotal study ELEVATE-TN conducted by Sharmann et al. were headache (39.9%), diarrhea (38.8%) and neutropenia (31.5%) in the acalabrutinib + obinutuzumab group, headache (36.9%), diarrhea (34.6%) and nausea (22.3%) in the acalabrutinib monotherapy group and neutropenia (45.0%), infusion-related reaction (39.6%) and nausea (31.4%) in the chlorambucil + obinutuzumab group. The median duration of exposure was 27.7 months in the acalabrutinib treatment groups vs. 5.6 months in the chlorambucil group.[11]

The most commonly observed AEs (any grade) in the pivotal study ASCEND conducted by Ghia et al. were headache (22%), neutropenia (19%) and diarrhea (18%) in the acalabrutinib group, diarrhea (47%), neutropenia (44%) and thrombocytopenia (18%) in the I-R group and neutropenia (34%), fatigue (23%) and infusion-related reaction (23%) in the B-R group. The median duration of exposure was 15.7 months in the acalabrutinib treatment group vs. 11.5 months in the investigator's choice group.[15]

Please refer to current SmPC of acalabrutinib (Calquence®) for expected AEs and thus for dose modification procedures.

1.2.5. Current status of market authorization in the European Union

The European Commission granted a marketing authorization valid throughout the European Union for acalabrutinib (Calquence®) in November 2020.

It is indicated as monotherapy or in combination with obinutuzumab for the treatment of adult patients with treatment-naïve CLL and is indicated as monotherapy for the treatment of adult patients with CLL who have received at least one prior treatment.

1.3. Bleeding events

Due to the mostly elderly CLL patient population, CLL patients often suffer from multiple cardiovascular comorbidities including atrial fibrillation (AF), deep vein thrombosis (DVT) or pulmonary embolism (PE) which make anticoagulation mandatory.[3] Additionally, ischemic strokes occur in 80% of the elderly patients, that may also lead to initiation of secondary prophylaxis with anticoagulating agents.[4] The management of cardiovascular comorbidities represents a major challenge in patients with CLL, Several drugs are available for anticoagulation therapy including vitamin K antagonists (VKAs), unfractionated heparin and low-molecular-weight heparins. While VKAs are taken orally and act long-term, low-molecular-weight heparins require daily subcutaneous injections. Recently, new direct oral anticoagulants (DOAC), i.e., factor Xa inhibitors (edoxaban, rivaroxaban, apixaban) or thrombin-inhibitors (e.g., dabigatran) have become available and extend treatment options.

In cancer patients, venous thromboembolism (VTE) treatment is associated with high risk of bleeding complications and must be monitored carefully.[5] In cancer patients treated with edoxaban, the rate of major

bleeding events was 6.9% as shown in the HOKUSAI trial (NCT02073682).[6] Furthermore, in non-cancer patients with atrial fibrillation receiving dabigatran, the rate of major bleeding events was around 3.7%.[7]

Early clinical studies have shown a greater bleeding risk in patients treated with BTKis.[10,11,15] Any grade hemorrhages could be found in ~48% patients treated with ibrutinib or zanubrutinib, respectively. The use of VKAs and DOACS was not permitted during the ELEVATE-TN and ASCEND trial.[10,13]

Bleeding events in TN CLL patients treated with acalabrutinib occurred at any grade in 43% (41% grade 1-2) of patients treated with acalabrutinib + obinutuzumab and in 39% (37% grade 1-2) of patients treated with acalabrutinib monotherapy. The most common bleeding events were contusion in 24% of patients in the acalabrutinib + obinutuzumab and in 15% in the acalabrutinib monotherapy group as well as petechiae in 8% patients in the acalabrutinib + obinutuzumab and in 9% in the acalabrutinib monotherapy group. Grade 3 or higher bleeding events (2%) were equally observed in both acalabrutinib treatment groups (n=6). Five of six patients with grade 3 or higher bleeding events did also receive anti-thrombotic agents (n=2 aspirin or enoxaparin, n=1 clopidogrel or heparin). Subdural bleeding events occurred in one patient, which had two events (grade 1 and grade 2) in the acalabrutinib +obinutuzumab group.[11]

In the ASCEND study evaluating R/R CLL patients treated with acalabrutinib, bleeding events of any grade occurred in 26% of patients treated with acalabrutinib and 7% of patients treated with investigator's choice, respectively. Most common bleeding events were contusion and hematoma. Major hemorrhage occurred in two (1%) patients in the acalabrutinib group (one grade 3 and one grade 4 gastrointestinal hemorrhage) and in three (2%) patients in the investigator's choice group (I-R: grade 3 gastrointestinal hemorrhage, grade 3 hematuria; B-R: grade 3 hemorrhagic anemia and grade 3 tumor hemorrhage in one patient). No grade 5 bleeding events and intracranial hemorrhages occurred.[15]

2. Research Questions and Objectives

2.1. Research question

The non-interventional study (NIS) CICERO will explore acalabrutinib (+/- obinutuzumab) in adult CLL patients (irrespective of treatment line) who receive co-medication with DOACs (edoxaban, rivaroxaban, dabigatran, apixaban). The primary focus of the study is to investigate the incidence proportion of bleeding events.

Up to now, no systematic and prospective evaluation on interactions of BTKis and DOACs has been conducted. It is known, that cancer patients treated with edoxaban have a risk of 6.9% to experience a major bleeding event.[6] In non-cancer patients treated with dabigatran, major bleeding events occur in 3.7%.[7] In TN CLL patients treated with acalabrutinib (+/- obinutuzumab), grade 3 or higher bleeding events were observed in about 2%.[11] In R/R CLL patients treated with acalabrutinib, major hemorrhage occurred in two (1%) patients (grade 3 and 4).[15] Only one retrospective cohort study evaluated the risk of major bleeding events in 30 patients with B-cell lymphoma treated with ibrutinib and DOACs. Major bleeding events, defined as grade 3 or 4 were detected in 16.6%.[16] Nevertheless, in Germany, a majority of physicians is reluctant to use BTKis in patients undergoing comedication with DOACs, therefore denying these patients an effective and otherwise safe treatment and have to choose from other, potentially less tolerable treatment options like e.g. FCR. Because the overall rate of anticipated bleeding events is lower with acalabrutinib compared to ibrutinib, we designed this study to systematically evaluate the bleeding risk in this patient population to provide more reliable evidence for clinical decision-making.

2.2. Objectives of the Study

The objective of this NIS is to evaluate safety with the focus on bleeding events in adult patients with CLL treated with acalabrutinib (+/- obinutuzumab) and co-medication with DOAC in a real-world setting.

2.2.1. Safety Objectives

- Assess bleeding events in patients receiving acalabrutinib and concomitant treatment with DOAC

Primary endpoint

- Incidence proportion of major bleeding events according to Schulman et al.[17]
  - i.e., fatal (contributes to death) and/or symptomatic in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) and/or causing a decrease in hemoglobin of 2 g/dL (1.24 mmol/l) or more or requires a transfusion of 2 or more units of whole blood or red blood cells.

Key secondary endpoints

- Incidence proportion of clinically relevant non-major (CRNM) bleeding events
  - i.e., bleeding that does not meet the criteria for major bleeding according to Schulman et al.[17] but is associated with the need for medical intervention and/or personal contact with a physician and/or hospitalization or increase in level of care.[21]
- Incidence proportion of major (according to Schulman et al.[17]) and/or CRNM bleeding events
- Incidence proportion of major bleeding according to Ghia et al.[15]
  - i.e., any serious OR grade ≥3 hemorrhage OR central nervous system (CNS) hemorrhage of any grade, excluding immune thrombocytopenic purpura

Secondary endpoints

- Incidence proportion of any bleeding event
- Time to first occurrence of major (according to Schulman et al.[17]) bleeding events
- Incidence proportion of CNS bleeding events

- Assess safety in patients receiving acalabrutinib and concomitant treatment with DOAC

  Secondary endpoints

  - Mortality from all causes during acalabrutinib therapy

- Assess safety in patients receiving acalabrutinib and concomitant treatment with DOAC in terms of interactions with effectiveness of DOAC

  Secondary endpoints

  - Rate of any new or recurrent ischemic stroke or arterial systemic embolism or venous thromboembolic events
  - Rate of VTE-related death

2.2.2. Effectiveness Objectives

- Assess effectiveness of acalabrutinib in patients treated with a DOAC

  Secondary endpoints

  - ORR, defined as proportion of patients with partial response or better as best response to acalabrutinib therapy
  - PFS, defined as time from start of acalabrutinib to occurrence of progressive disease or death from any cause, whichever comes first
  - OS, defined as time from start of acalabrutinib to death from any cause

2.2.3. Other Objectives

- Assess parameters of acalabrutinib therapy decision making

Secondary endpoints

- Frequency of distinct parameters affecting therapy choice

- Describe treatment in detail

  Secondary endpoints

  - Details of previous therapies
  - Details of acalabrutinib (+/- obinutuzumab) treatment and treatment with DOAC
  - Frequency of concomitant medication other than DOAC

2.2.4. Exploratory Objectives

Not applicable

2.3. Rationale for the Selection of Methods

The choice of this methodical approach results from the character of a NIS to observe the performance of patient and treating physician in routine clinical practice in the context of the observed treatment.

3. Study Design

3.1. Regulatory Setting

This study is a NIS according to Section 4 (23) Sentence 3 German Medicinal Products Act (AMG § 4 Abs. 23 Satz 3) to document data from routine clinical practice regarding 1st- or later-line therapy of patients with CLL treated with acalabrutinib (Calquence®) (+/- obinutuzumab), a product of AstraZeneca, additionally under treatment with DOAC (i.e., edoxaban (Lixiana®) or rivaroxaban (Xarelto®) or dabigatran (Pradaxa®) or apixaban (Eliquis®).

This study is neither a clinical trial nor a phase IV trial since the use of the observed treatment and examinations are not determined by a defined study protocol but follow routine clinical practice.

In accordance, the assignment of the patient to the therapeutic strategy is not decided in advance by a trial protocol but follows current routine clinical practice and the prescription of the medicine is clearly separated from the decision to include the patient into the study. There are no mandatory dose regimens or medical procedures defined in this observational plan. Patients will be treated in clinical routine with Calquence® (acalabrutinib) according to current SmPC and are additionally under treatment with DOAC (edoxaban (Lixiana®) or rivaroxaban (Xarelto®) or dabigatran (Pradaxa®) or apixaban (Eliquis®)) due to an underlying concomitant disease according to current SmPCs.

The medical professionals are free to decide which diagnostic measures they perform (in accordance with routine clinical practice), which patients they treat with the drug documented in this study (treatment according to current SmPC) and how to monitor the course of treatment and which concomitant medications they prescribe. Appointments between the treating physician and the patient will be scheduled individually according to clinical necessity. The requirement during the conduct of this NIS is to document medical decisions and procedures in the electronic case report form (eCRF) according to the observational plan. The concept and conduction of this NIS and its documentation procedure will not affect routine clinical practice in any aspect. Patient treatment, including diagnosis and follow-up, is solely accountable to the respective treating physician.

3.2. Description of Study Design

Planned recruitment period: In total, 50 patients will be enrolled (excluding screening failures, patients with off-label use and with violation of inclusion/exclusion criteria identified after treatment start) in 20

oncological/hematological sites in a time period of 18 months. For details on patient enrollment and specification of sites refer to sections 4.1 and 4.2, respectively.

Treatment observation period: i.e., time period during acalabrutinib administration
For details on documentation procedures please refer to section 5.

Follow-up period: i.e., period from EOT until End of Study (EOS)
For details on documentation procedures please refer to section 5.

End of study (EOS): The end of study will be 12 months after LPI.

The study design is depicted in Figure 6.

3.3. Duration and Termination of the Study

3.3.1. Timelines and Regular End of Study

In total, study duration is planned to be 30 months.

Recruitment (time from FPI to LPI) is planned to start Q3 2022 and to last until Q1 2024, i.e., 18 months.

Regular end of study (EOS) is planned to be in Q1 2025. The regular EOS is defined as last patient last visit, however latest 12 months after LPI.

Please refer to Figure 6.

Planned start of data collection (FPI):	Q3 2022
Planned end of enrollment (LPI):	Q1 2024
Planned end of data collection (LPO/LPLV):	Q1 2025
Planned end of study (EOS):	Q1 2025
Database lock (DBL):	2 months after LPO/EOS
Final analysis (FA):	4 months after DBL
Final study report (FSR):	4 months after FA
Presentation/ Publication of final results:	after FA

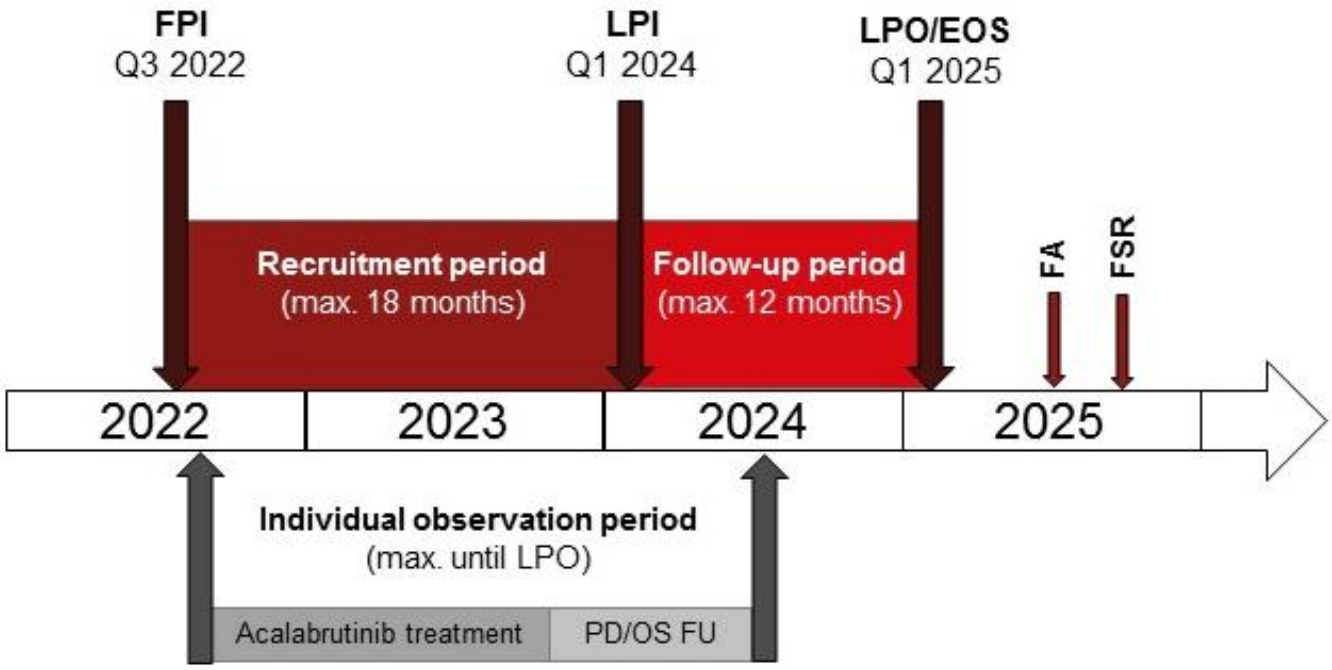

*Figure 6**: Expected time schedule***

According to the current SmPC of Calquence®, acalabrutinib should be administered until PD or unacceptable toxicity.

Patients will be observed from enrollment into CICERO until EOS. Treatment with acalabrutinib will be observed during acalabrutinib administration. Survival will be followed up for latest 12 months after LPI.

3.3.2. Premature End of Study

The sponsor reserves the right to terminate the study prematurely in its entirety or at a specific site at any time.

Reasons for premature study termination in its entirety may include (but are not limited to)

- Any safety concerns that invalidate the earlier positive benefit-risk profile of substance,
- Determination of unexpected, significant, or unacceptable risk to patients.

Reasons for premature study termination at a specific study site may include (but are not limited to):

- Non-compliance with data entry requirements,
- Non-recruitment,
- Falsification of data, or
- Requests by regulatory authorities to suspend or terminate the study.

3.3.3. Individual End of Study Participation

The planned individual time of study participation per patient will be from signature of the patient informed consent until death or EOS, whatever comes first.

However, patients are free to withdraw consent for the study at any time without providing reasons and without having any disadvantages for consecutive therapies.

3.4. Biomarker profiling – Decentral Biobank

Not Applicable

4. Setting

4.1. Patient Population

4.1.1. Patient Enrollment

Eligible patients with CLL who have already been scheduled to receive acalabrutinib (+/- obinutuzumab) and co-medication with DOAC as 1st- or later-line treatment by their treating physician prior to enrollment into CICERO.

Patients have to provide written informed consent to capture and release data concerning their treatment in a pseudonymized manner (using patient ID and year of birth) and insight into personal data on site by authorized persons before enrollment.

Inclusion of patients will be prospectively, except for patients with 6 weeks of acalabrutinib (+/- obinutuzumab) treatment prior to inclusion. Those patients may be retrospectively included within 6 weeks after the start of therapy.

4.1.2. Inclusion Criteria

Patients must comply with all the following criteria to be enrolled in the study:

- Aged 18 years or older.
- Patients with chronic lymphocytic leukemia (CLL) decision for treatment with acalabrutinib (+/- obinutuzumab) according to current SmPC as assessed by the treating physician or already started treatment with acalabrutinib (+/- obinutuzumab) no longer than 6 weeks ago.
- Other concomitant disease resulting in medical need of or already under treatment with direct oral anticoagulant (DOAC) treatment with edoxaban (Lixiana®) or rivaroxaban (Xarelto®) or dabigatran (Pradaxa®) or apixaban (Eliquis®) according to the respective current SmPC.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Signed written informed consent.

4.1.3. Exclusion Criteria

Patients are not eligible, if any criterion is met:

- Combination of acalabrutinib with other substances than obinutuzumab for CLL treatment
- Participation in an interventional clinical trial with acalabrutinib.

4.1.4. Inclusion and exclusion criteria violation after informed consent

4.1.4.1. Before start of first- or later-line treatment (Screening Failures)

Screening failures are defined as patients with signed informed consent but who do not meet all inclusion and exclusion criteria, identified before start of 1st- or later-line treatment with acalabrutinib. Documentation will be stopped upon identification and EOS will be documented accordingly. Screening failures will be replaced. Sites are not remunerated for screening failures.

4.1.4.2. After start of first- or later-line treatment (e.g., Off-label use)

Documentation will be stopped upon identification of off-label use (for definition refer to chapter 4.3.1). Off-label patients will be replaced. For these patients ‘off-label use’ should be documented as reason for EOS in the eCRF. Sites are not remunerated for off-label patients.

The violation of any inclusion or exclusion criteria (IC/EC) identified after start of 1st- or later-line treatment with acalabrutinib that do not meet definition of off-label use will be documented. Documentation of respective patients will be stopped upon identification. Patients will be replaced. For these patients 'Violation of IC/EC identified after treatment start' should be documented as reason for EOS in the eCRF. Sites are not remunerated for those patients.

4.2. Specification of Study Sites and Number of Patients

The study will be conducted at approximately 20 oncological/hematological sites (office-based medical oncologists/hematologists, outpatient-centers, and (university) hospitals) distributed over all regions of Germany. The study aims to include 50 adult patients with CLL (excluding screening failures and patients with off-label use or violation of IC/EC identified after treatment start) and treatment decision for acalabrutinib (+/- obinutuzumab) additionally under treatment with DOAC.

4.3. Treatment Setting

Treatment decision has been made prior to patient's study entry and treatment will be administered at the treating physician´s discretion according to current SmPC and as per routine clinical practice. All information on dosing will be collected in the eCRF. Acalabrutinib (+/- obinutuzumab) and DOACs are prescribed in accordance with the terms of the marketing authorization.

Acalabrutinib as monotherapy or in combination with obinutuzumab is approved for treatment of adult patients with previously untreated CLL. Acalabrutinib monotherapy is approved for the treatment of adult patients with CLL, who received at least one prior therapy.

In CICERO, treatment with acalabrutinib (+/- obinutuzumab) additionally under treatment with DOACs will be observed in patients with TN or previously treated (at least one prior therapy) CLL.

Please refer to current *SmPC(s)* for information on study medication:

Acalabrutinib (Calquence®)

Obinutuzumab (Gazyvaro®)

Patients are to be treated at any time according to current version of SmPC of acalabrutinib (Calquence®). Dose modifications decided by the treating physician will not be judged as off-label use.

SmPC updates will overrule the respective sections of this observational plan, which is based on the current version of the acalabrutinib SmPC at study start.

4.3.1. Off-label use definition

'Off-label use' will be judged at study inclusion (signing of informed consent form (ICF) / first time of acalabrutinib administration. In this study, off-label use is defined as:

- Treatment of patients with cancer other than CLL.
- Treatment of patients with acalabrutinib (Calquence®) and a combination partner other than obinutuzumab to treat CLL.

5. Documentation of Patient Data

The physician or delegate is asked to document medical data, diagnostic and monitoring procedures (e.g., lab parameters) as well as AEs and SAEs in the eCRF according to the observational plan (for data collection see Table 5). Documentation procedures do not influence the routine course of therapy or treatment decisions.

5.1. Documentation Procedure

Prior to inclusion, the treating physician or delegate will ensure that inclusion and exclusion criteria are met. The patient will be informed about the study by the treating physician. If the patients decide to participate in CICERO, they have to give written informed consent. One copy will remain with the patient. Another copy will remain at the study site. The physician / site personnel will confirm the correct procedure and the date of informed consent in the eCRF. This confirmation is a prerequisite to document patient data.

Patient data will be documented online in the eCRF. The eCRF will be provided by iOMEDICO (please refer to sections 8.2, 9.1). Patient data from inclusion until the individual end of study participation due to any cause, however not longer than 12 months after the inclusion of the last patient (LPI), will be documented.

The eCRF will be divided into the following sections:

1. Enrollment including:
    a. Confirmation of informed consent
    b. Patient Eligibility (check of inclusion and exclusion criteria)
    c. Demographics
2. Baseline
3. Treatment observation (cycle-based)
4. End of treatment
5. Follow-up
6. End of study participation

5.2. Data Sources

Data collected in this study will be transferred from patients' medical records and project-specific information and documentation sheets to a secure web-based eCRF, provided by iOMEDICO for the duration of this study (please refer to sections 8.2, 9.1).

For each patient enrolled in this study, i.e., signed informed consent form (ICF), data have to be entered in the eCRF by the treating physician or a person designated by the treating physician and the eCRF has to be signed using a specific password assigned by iOMEDICO.

All entries in the eCRF should be substantiated by entries in the original patient file. Patient names are not to be documented in the eCRF or on any other document that will be sent to iOMEDICO.

The observational plan only allows for documentation of data derived from tests and examinations performed in routine clinical practice and the bleeding assessment tool as documentation aid. All data collected in the context of this study are confidential.

5.3. Schedule of Documentation

Data will be documented in accordance with routine clinical practice.

Table 5: ***Data collection plan***

	Baseline	Treatment observation period (cycle-based)	End of treatment (incl. 30 days of safety FU)	Follow-up period	End of study participation
Patient Informed Consent	x				
Inclusion / Exclusion criteria	x				
Demographics	x				
Disease anamnesis, Disease characteristics, Disease stage	x				
Laboratory parameters	x	x	x		
Medical history and concomitant diseases (including other malignant diseases)[1]	x				
Charlson Comorbidity Index (CCI)	x				
Concomitant medication (anti-anemia, anti-thrombocytopenia, anti-coagulation (other than DOAC), anti-emetic, anti-diarrhea, anti-infection as well as anti-hyperuricemic)[2]	x	x	x		
Physical examination, including assessment of body weight and height[3]	x	x	x		
Performance status (Karnofsky or ECOG)	x	x	x		
Reason for acalabrutinib therapy decision	X				
Prior treatment(s)	X				
Patient questionnaire for bleeding events (adapted to the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool)[4]	X[8]	x	x		
Bleeding events including those based on the patient questionnaire	X	x	x		

Details on treatment with acalabrutinib (+/- obinutuzumab)[5]		x			
Details on treatment with DOACs[5]		x			
Details on surgeries or radiotherapies during acalabrutinib treatment		x			
Response evaluation and lymph node / organ assessment[6]		x	x		
Date and reason for discontinuation of acalabrutinib treatment			x		
Date and reason for discontinuation of DOAC treatment			x		
(Serious) adverse events[7]	x	x	x		
Serious adverse drug reactions (SADRs) related to acalabrutinib[7]		x	x	x	
Date and reason for end of study participation					x
Progression and Survival status				x	x

1. Medical history should be documented for any relevant (defined as need for treatment or control measures) preexisting and concomitant diseases and surgeries. Medical History and CCI will be not checked for congruent data entries.
2. Documentation of concomitant medication is limited to mentioned substance classes.
3. Height only at baseline.
4. PROs will be assessed at every visit in routine care at the treating physician until treatment with acalabrutinib is discontinued due to disease progression or any other reason. Questionnaire will be distributed by study site. Patients will be asked if distinct events occurred in the time between the last visit until the current visit and discuss the questionnaire with the physician to determine if any AE occurred. This questionnaire will only be used as documentation aid and will not be transferred to the eCRF but is seen as source document. Distribution and fill-out date will be tracked in the eCRF
5. Data will be collected until the end of last cycle with acalabrutinib administration.
6. It is recommended to use the local medical standards and if possible according to the current guidelines[8]. Status of disease progression should be documented until discontinuation of acalabrutinib treatment due to PD, unacceptable toxicity or other reasons.
7. AEs (incl. ADRs) will be documented continuously after signature of informed consent form, during acalabrutinib treatment until 30 days after discontinuation of acalabrutinib. Thereafter only related SAEs have to be reported. For retrospectively included patients, all (S)AEs documented in the medical records that occurred from start of therapy until enrolment have to be reported additionally.
8. Bleeding assessment tool will be distributed at inclusion for retrospectively included patients only.

5.4. Documentation Variables

5.4.1. Baseline Documentation

The following parameters will be documented at baseline:

- Presence and date of signed informed consent
- Inclusion and exclusion criteria
- Demographics: Year of birth, sex, ethnicitiy
- Disease anamnesis, Disease characteristics, Disease stage
    - Date of initial diagnosis of CLL
    - Prior antineoplastic therapies (systemic treatments, radiotherapies, transplantations), substances for antineoplastic treatments, type of transplantation
    - Molecular genetics (*TP53, IGHV status, complex caryotype, del(17p3), del(11q))*
    - Bone marrow examination (e.g., presence of lymphocytosis (i.e., >30% of nucleated cell in BM aspirate)
    - Stage at initial diagnosis (Rai and Binet)
    - CLL-IPI score at initial diagnosis
    - Organ involvement (liver (hepatomegaly), lymph nodes, spleen (splenomegaly), with number of involved regions)
    - Current treatment for autoimmune phenomena
- Laboratory parameters for evaluation of CLL, including leucocytes, thrombocytes, hemoglobin, lymphocytes, ALT, AST, total bilirubin, creatinine, ß2MG
- Medical history and concomitant diseases: Documentation of all relevant (defined as need for treatment or control measures) pre-existing and concomitant diseases.
- Charlson Comorbidity Index (CCI)
- Concomitant medication with DOAC
- Concomitant medication with non-DOAC (limited to anti-anemia, anti-thrombocytopenia, anti-coagulation (other than DOAC), anti-emetic, anti-diarrhea, anti-infection as well as anti-hyperuricemic)
- Physical examination: Body weight and height,. Clinically relevant abnormalities observed at baseline should be entered as part of the medical history.
- Performance status (Karnofsky or ECOG).

For further details please refer to section 13.3 in appendices.

- Reason for therapy decision (Physician questionnaire)

For further details please refer to section 13.5 in appendices.

- Patient questionnaire

  Patient questionnaire for bleeding events adapted to the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH – BAT).[18–20]
  Paper-based questionnaire will be distributed by study site to the patient at inclusion only for retrospectively included patients.

  For further details, please refer to section 5.4.2, 6, 9.2 and section 13.4 in appendices.

- Safety reporting: AEs and SAEs will be documented continuously from time of signature of informed consent form throughout the treatment period with acalabrutinib until 30 days after the time of last administration of acalabrutinib or the start of new anticancer therapy (whichever comes first). After this period, investigators

should report SAEs or other AEs of concern that are assessed by investigator to be causally related to prior study drug treatment (please refer to section 6 for details). The safety reporting for retrospectively included patient is in detail defined in section 6. The following safety laboratory parameters will be documented according to clinical practice: hemoglobin, thrombocytes, leucocytes, erythrocytes, hematocrit, lymphocytes, neutrophils (absolute neutrophil count (ANC)), neutrophils relative (%), white blood count (WBC), ß2MG, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean platelet volume (MPV), partial thromboplastin time (PTT), activated partial thromboplastin time (aPTT) international normalized ratio (INR), red blood cell distribution width (RDW), thrombin clotting time (TCT), thrombin time (TT), creatinine, glomerular filtration rate (GFR), alkaline phosphatase, bilirubin total, uric acid, aspartate transaminase (AST) (glutamic oxaloacetic transaminase (GOT)), alanine transaminase (ALT) (glutamic pyruvate transaminase (GPT)) and gamma-glutamyltransferase (gamma-GT) and tests on coagulation monitoring and platelet count/functional tests (including reagents and assay provider, if applicable), if conducted in the clinical routine practice by the documenting study site.Documentation During Treatment

The following parameters will be documented during the acalabrutinib treatment. Documentation should be performed after each cycle in a timely manner.

- Physical examination, please refer to section 5.4.1

  Clinically relevant abnormalities appearing during therapy with acalabrutinib should be reported as AE.
- Performance status, please refer to section 5.4.1
- Concomitant medication, please refer to section 5.4.1
- Details on treatment with acalabrutinib (+/-obinutuzumab) and DOACs: Start and end date and dose will be documented. This includes the documentation of treatment interruptions and dose modifications with reasons.
- Response evaluation: Response will be assessed by the treating physician on the basis of
  - CLL specific laboratory parameters
  - Imaging (Computed tomography (CT), magnet resonance imaging (MRI), sonography)
  - Lymph node examination

    as per local routine and if possible according to current guidlines[8]. Response should be documented until discontinuation of acalabrutinib treatment due to PD, unacceptable toxicity, or other reasons. In case acalabrutinib treatment was terminated for another reason than PD, response / PD should be documented in the follow-up period.
- Safety reporting: please refer to section 5.4.1
- Patient questionnaire

  Patient questionnaire for bleeding events adapted to the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH – BAT).[18–20]
  Paper-based questionnaire will be distributed by study site to the patient at every visit in routine care at the treating physician. Patients will be asked if distinct events occurred in the time between the last visit in routine care until the current visit in routine care and discuss the questionnaire with the physician to determine of any AE occurred. This questionnaire will only be used as documentation aid and will not be transferred to the eCRF but is seen as source document. Distribution and fill-out date will be tracked in the eCRF.

  For further details, please refer to section 9.2 and section 13.6 in appendices.

5.4.2. Documentation at the End of Treatment

At the end of treatment with acalabrutinib, the following variables will be documented:

- Physical examination, please refer to section 5.4.1

  Clinically relevant abnormalities appearing during therapy with acalabrutinib should be reported as AE.
- Performance status, please refer to section 5.4.1
- Concomitant medication, please refer to section 5.4.1

- Safety reporting, please refer to section 5.4.2
- Response evaluation, please refer to section 5.4.2
- ADRs will be reported until EOS
- Reason and date for discontinuation of treatment within the study (acalabrutinib, obinutuzumab if applicable, DOAC)

The following reasons may trigger the end of treatment documentation within the study:

- Progressive disease
- (Serious) Adverse event
- Other
  - Lost to follow-up
  - Off-label use
  - Pregnancy
  - Site terminated by sponsor
  - Study terminated by sponsor
  - Withdrawal of informed consent by subject
  - Violation of IC/EC, identified after treatment start
  - Other

5.4.3. Follow-up Documentation

After the end of treatment observation, the following variables will be documented:

- Response evaluation will be continued as per local standard for patients who have not progressed at the end of treatment until PD.
- Survival status
- ADRs will be reported until EOS

Follow-up documentation will be performed at least all 3 months with the exemption of response documentation, which should be done in a timely manner to evaluation.

5.4.4. End of Study Participation

- Reason and date for end of study participation will be documented for each patient

The following reasons may trigger study discontinuation

- Death
- Study completion
- Other
  - Lost to follow-up
  - Off-label use
  - Screening failure
  - Study terminated by sponsor
  - Site terminated by sponsor
  - Violation of IC/EC, identified after treatment start
  - Withdrawal of informed consent by subject
  - Other
- Survival Status

6. (Serious) Adverse Event Management and Reporting

All adverse events (serious and non-serious) will be documented continuously during acalabrutinib administration also for retrospectively included patients. All (S)AEs documented in the medical records that occurred from start of therapy until enrolment have to be reported additionally.

6.1. Definitions

6.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence (or worsening of any pre-existing) in a patient administered a medicinal product, regardless of whether it has a causal relationship with this treatment. An AE can therefore be the appearance of (or worsening of pre-existing) any unfavorable sign (including an abnormal laboratory finding), symptom, or medical condition.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of study medication) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received study medication.

The term AE is used to include both serious and non-serious AEs.

6.1.2. Adverse Drug Reaction (ADR)

An adverse drug reaction (ADR) is defined as response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label-use, overdose, misuse, abuse and medication errors.

6.1.3. Serious adverse event (SAE)

A SAE is an AE that fulfills one or more of the following criteria:

- Is fatal or life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration of condition (i.e., to perform study-related assessments)
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above.

Any suspected transmission of an infectious agent via a medicinal product is also considered an SAE.

Special attention should be paid to Hy´s Law cases as they may be subject to expedited reporting. Cases where a patient shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3xULN together with total bilirubin ≥2xULN (referred to as Hy´s Law cases) may need to be reported as SAEs.

Progression of the malignancy under study (excluding fatal outcomes) should not be reported as an SAE. In case of fatal disease progression leading to death during acalabrutinib treatment and 30 days thereafter, this has to be reported as SAE.
AEs separate from the progression of malignancy (example: deep vein thrombosis at the time of progression or haemoptysis) will be reported as usual.

Comment to Seriousness Assessment for Invasive and Malignant Cancers:

Adverse Events (AEs) for malignant tumors reported during this study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. Note that this instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the medicinal product under study and is not the development of new or progression of existing metastasis to the tumor under study). If the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur.
Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

6.1.4. Serious Adverse Drug Reaction (SADR)

A serious ADR is an adverse drug reaction which fulfils one of the SAE criteria.

6.1.5. Explanatory Notes concerning (S)AE criteria

An AE/SAE does not include the following:

- Medical or surgical procedures. The condition that led to the procedure may be an AE and should be reported.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective pre-planned surgery, social and/or convenience admissions).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the start of treatment with acalabrutinib (after enrollment) or, in the case of retrospectively enrolled patients, before the consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history case report form (eCRF) (if applicable).
- Death is an outcome of an AE, and not an AE in itself. Therefore, if death occurred, the event that led to death needs to be reported as an SAE.
- Whenever possible a diagnosis should be reported instead of underlying symptoms.

6.1.6. Special Situations

In addition, the following special situations are reportable

- Pregnancy and suspected pregnancy of a female patient occurring while the patient is receiving acalabrutinib in combination with DOAC. *(-> Reporting see Chapter Documentation and Reporting of exposures during pregnancies and during the nursing period)*
- Any adverse reactions which occur in infants following exposure from breastfeeding *(-> Reporting see Chapter Documentation and Reporting of exposures during pregnancies and during the nursing period)*
- Medication error
- Overdose, abuse, misuse
- Occupational exposure
- Lack of therapeutic efficacy
- Off-label-use (defined in section 4.1.4.2)

6.2. Reporting of Adverse Events

All AEs occurring after signature of informed consent form (ICF) and during acalabrutinib treatment must be documented in the eCRF until 30 days after the last administration of acalabrutinib or initiation of new anticancer therapy, whichever comes first. Thereafter only SAEs with causal relationship to acalabrutinib have to be documented. After the signing of the ICF and prior to the first dose of study treatment all SAEs, regardless of causality, must be reported. For retrospectively enrolled patients the reporting period begins with the start of treatment with acalabrutinib, i.e., all (S)AEs that occurred from the start of the therapy with acalabrutinib until inclusion in the study must be documented and reported additionally.

Causality:

Physicians should determine whether the occurrence of an AE is related or not related to the administered medicinal product by taking into consideration the following guidance:

- Related: The temporal relationship of the AE to drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- Not related: There is no reasonable possibility that the administrated drug caused the event, there is no temporal relationship between the drug administration and event onset, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Duration:

For all AEs the start and stop dates of the event should be provided.

Action Taken:

Action taken with study medication as a result of an AE should be reported as applicable (e.g., discontinuation or reduction of study medication, as appropriate).Outcome:

Outcome of the event has to be reported.

Information on not resolved AEs has to be updated until the study is closed for documentation (database lock) or until a patient withdraws informed consent for study participation.

Grading of Events:

AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline. AEs that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades as follows:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

A Semi-colon indicates ‘or’ within the description of the grade.

Note: If the CTCAE severity grade varies during the course of the AE and the clinical finding/situation fulfills any of the conditions in the grade descriptions for more than one severity grade level, than the AE should only be recorded once with the most severe CTCAE grade (not as several AEs of different CTCAE-grades).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Sections 6.1.3. An AE of severe intensity need not necessarily be

considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets one of the criteria shown in Section 6.1.3. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE if it satisfies one of the criteria shown in Section 6.1.3.

6.3. Reporting of Serious Adverse Events

Any AE with a fatal outcome and any initially occurring SAE, as well as updated information for all SAEs must be reported within one day i.e., immediately but **no later than 24 hours** after becoming aware of it. Data have to be entered in the Adverse Event screen in the **eCRF.** The SAE data documented and saved in the eCRF are automatically transferred to the applicable drug safety departments of AstraZeneca and iOMEDICO.

Further information can be requested by the drug safety department for completion of a case evaluation. Required information has to be provided by the study site.

Only in case of eCRF system failure the paper-based SAE Report Form should be used and sent to

iOMEDICO AG
Fax: [redacted]

within 24 hours of awareness. Once the eCRF is available again, SAE data, previously reported on the SAE Report Form, have to be entered on the eCRF Adverse Event Page.

6.4. Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) are events that may not typically be considered to meet the regulatory criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the timely review of safety data and narrative (may be requested by the competent authority or the sponsor). It can be e.g., a non-serious non-specific start of an event, which may be an early manifestation of a serious potential risk.

The same SAE reporting form, assessment and reporting timelines apply to AESIs. For reporting purposes, they need to be treated as if they were serious events even when these events are non-serious and do not meet seriousness criteria The following events are adverse events of special interest (AESIs) for patients exposed to acalabrutinib, and must be reported to the sponsor expeditiously, irrespective of regulatory seriousness criteria or causality.

For details refer to section 13.3 in the appendix. It is within the responsibility of the investigator (i.e., principal investigator of the respective study site) to assess whether an adverse event fulfills the criteria for an AESI and to flag this accordingly in the eCRF.

6.5. Documentation and Reporting of exposures during pregnancies and during the nursing period

All pregnancies and breastfeeding periods of a female patient existing or newly occurring during acalabrutinib administration or the following 30 days after the last acalabrutinib administration have to be reported within 24 hours after knowledge by sending the Pregnancy Report Form to

iOMEDICO AG
Fax: [redacted]

Additionally, the information has to be entered on the pregnancy report page of the eCRF.

All pregnancies reported within the study should be followed until pregnancy outcome.

Any abortion or stillbirth should be classified as SAE and recorded in the AE section of the eCRF within 24 hours after becoming aware of it.

6.5.1. Reporting of Special Situations

Other Special Situations (refer to section 6.1.6 for details) must be documented in the eCRF within 15 calendar days after learning of the situation.

6.6. Clinical laboratory abnormalities

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, abnormal laboratory parameters or tests should be classified as AE if they

- are clinically relevant, i.e.
- present with clinical signs and/or symptoms
- require a therapeutic intervention or
- lead to a dose reduction or temporary or permanent discontinuation of acalabrutinib

If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

Special attention should be drawn to safety laboratory parameters (see section 5.4.2).

It is within the physician's decision if a laboratory abnormality should be reported as AE or not.

6.7. Patient Questionnaires

Patient questionnaires for bleeding events will not be checked for hidden adverse events. The treating physician uses the questionnaire in dialog with the patient to determine whether (S)AEs have occurred that need to be transferred to the medical record and the eCRF (refer to section 9.2 for the management of patient questionnaires).

7. Data Analysis and Statistics

7.1. Sample Size Calculation

Due to the exploratory character of the study, no formal sample size calculation is conducted, and no hypotheses will be tested. N=50 patients will be enrolled.

For the primary endpoint, the proportion of patients with major bleedings is expected to be 2-5% based on the observed proportion of patients with major bleeding in the pivotal studies ASCEND and ELEVATE TN as well as other data available of DOAC treated cancer and non-cancer patients. In cancer patients treated with edoxaban the proportion of patients with major bleeding events was 6.9% as shown in the HOKUSAI trial (NCT02073682)[6] and in non-cancer patients with atrial fibrillation receiving dabigatran, the proportion was around 3.7%.[7]

Therefore, for the primary endpoint, the following precision (95% confidence interval (CI)) can be reached with this sample size:

Sample size	**Proportion of patients with major bleedings**	**95% CI (exact Clopper-Pearson)**
50	2%	0.05% - 10.65%
50	3%	0.22% - 12.22%
50	4%	0.49% -13.71%
50	5%	0.84% - 15.15%

Because this is a single-arm observational study, we cannot conduct any direct comparisons. However, results of the primary endpoint will be discussed within the context of the existing body of evidence on other BTKis in CLL, other CLL treatments as well as data available from DOAC treatment only in cancer patients and additionally in non-cancer patients.

7.2. Analysis Populations and Subgroups

7.2.1. Primary Analysis Population: Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all included patients who received at least one dose of acalabrutinib in-label (compare section 4.1.4.2) and DOAC. Patients for whom a violation of inclusion/exclusion criteria was detected after treatment start will be excluded from the FAS. This population is the primary analysis population and is relevant for all analyses, including safety analyses.

7.2.2. Examination of Subgroups

Effectiveness parameters (ORR, PFS, OS) will be analyzed in the subgroup of patients enrolled for first-line acalabrutinib (+/- obinutuzumab) therapy vs. pre-treated patients enrolled for later-line acalabrutinib therapy.

7.3. Statistical Analysis

7.3.1. Interim Analyses

No interim analyses are scheduled.

7.3.2. General Description of Methods

All documented parameters will be analyzed descriptively.

For continuous variables the number of observations, mean, standard deviation, minimum, 25th quartile, median, 75th quartile and maximum will be presented. For categorical variables frequencies and percentages will be given.

The Kaplan-Meier method will be used for time-to-event analyses (PFS, OS).

Competing risk analysis will be conducted for the endpoint “Time to first occurrence of major bleeding event”.

Analyses will be performed for all available data. No imputation for missing data will be conducted.

If size of analysis populations (FAS, SAF) differs by more than 10%, main patient and disease characteristics will be provided for each population.

7.3.3. Analysis of Effectiveness Endpoints

Definitions:

Overall Response Rate: ORR is defined as proportion of patients with partial response or better for best response obtained in any evaluation during acalabrutinib treatment according to institutional standards.

Progression-Free Survival: PFS is defined as time from onset of acalabrutinib therapy to first occurrence of progressive disease or death, whichever comes first. It will be analyzed using Kaplan-Meier method. Data will be censored at date of last contact for patients alive without diagnosis of progressive disease at end of study.

Overall Survival: OS is defined as time from start of acalabrutinib treatment to death from any cause. It will be analyzed using Kaplan-Meier method. Data will be censored at date of last contact for patients alive at end of study.

Analyses:

The ORR and best responses will be presented with frequencies and percentages.

For PFS and OS, 1st quartile, median, 3rd quartile, and 6-, 12-, 18- as well as 24-months rates will be given together with 95% confidence limits. The frequency of events will be displayed. A Kaplan-Meier plot including numbers at risk will be presented.

7.3.4. Analysis of Safety Endpoints

Definitions:

Major Bleeding according to Schulman et al.: Bleeding is defined as major, if it is fatal (contributes to death) and/or symptomatic in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) and/or causing a decrease in hemoglobin of 2 g/dL (1.24 mmol/l) or more or requires a transfusion of 2 or more units of whole blood or red blood cells.[17]

Clinically relevant non-major bleeding: CRNM is defined as bleeding that does not meet the criteria for major bleeding according to Schulman et al.[17] but is associated with the need for medical intervention and/or personal contact with a physician and/or hospitalization or increase in level of care.[21]

Major bleeding according to Ghia et al.: Major bleeding is defined as any serious or grade ≥3 hemorrhage or CNS hemorrhage of any grade, excluding immune thrombocytopenic purpura.[15]

Analyses:

Frequencies and percentages will be presented for the following endpoints:

- Incidence proportion of patients with major bleeding event according to Schulman et al. (primary endpoint)
- Incidence proportion of patients with CRNM bleeding events (key secondary endpoint)
- Incidence proportion of patients with major (according to Schulman et al.) and/or CRNM bleeding events (key secondary endpoint)
- Incidence proportion of patients with major bleeding event according to Ghia et al. (key secondary endpoint)
- Incidence proportion of patients with any bleeding event
- Incidence proportion of patients with CNS bleeding event
- Mortality from all causes (patients who deceased during acalabrutinib therapy or within 30 days after last dose)
- Incidence proportion of patients with VTE-related death
- Incidence proportion of patients with any new or recurrent ischemic stroke or systemic arterial embolism or venous thromboembolic event

Time to first occurrence of major bleeding events according to Schulman et al.: Competing risk analysis (competing event: death) will be conducted. Time from start of acalabrutinib therapy to first occurrence of major bleeding according to Schulman et al. (event of interest) or death (competing event), will be calculated. Data will be censored at end of AE reporting period for patients alive without any major bleeding until this point in time. Cumulative incidence curves for major bleeding according to Schulman et al. and for death will be presented.

Details of acalabrutinib (+/- obinutuzumab) treatment and treatment with DOAC (secondary endpoint)

- Treatment duration of acalabrutinib: descriptive statistics
- Dose intensity of acalabrutinib treatment with reference to the SmPC (absolute and relative): descriptive statistics
- Dose modifications of acalabrutinib with reasons: frequencies and percentages
- Reasons for end of acalabrutinib treatment: frequencies and percentages
- Treatment duration of obinutuzumab: descriptive statistics
- Reasons for end of obinutuzumab treatment: frequencies and percentages
- Type of DOAC used (edoxaban, rivaroxaban, dabigatran and apixaban)
- Time from onset of DOAC to start of acalabrutinib therapy (descriptive statistics)

- Treatment duration of DOAC: descriptive statistics
- Dose modifications of DOAC with reasons: frequencies and percentages
- Reasons for end of DOAC treatment: frequencies and percentages
- Reasons for DOAC treatment: frequencies and percentages

Concomitant medication other than DOAC: Frequencies and percentages of concomitant medication (anti-anemia, anti-thrombocytopenia, anti-coagulation, anti-emetic, anti-diarrhea, anti-infection, anti-hyperuricemia medication) will be given.

7.3.5. Analyses of Exploratory Objectives

Definitions: *NA*

Analyses: *NA*

7.3.6. Analysis of Other Objectives

Definitions:

Treatment-Emergent Adverse Event (TEAE): an AE is classified as treatment-emergent, if it is temporally related to acalabrutinib, i.e., it occurred within the time frame from start of acalabrutinib treatment until 30 days after end of acalabrutinib treatment.

Analyses:

- Endpoints
  - Previous therapies: frequencies and percentages will be given for the
    - number of previous systemic CLL treatments
    - substances used for previous systemic CLL treatment by line of treatment
    - reason for discontinuation of previous systemic CLL treatment by line of treatment
    - proportion of patients with previous stem cell transplantation
    - type of previous stem cell transplantation
    - proportion of patients with previous radiotherapy
  - Acalabrutinib therapy decision parameter: frequencies and percentages of distinct parameters affecting therapy choice will be given.

7.3.7. Details on Analyses

- General
  - Number of patients per center (Descriptive statistics of number of patients per center, Frequencies of centers with n patients)
  - Disposition of patients (number of patients receiving allocated treatment, number of patients not receiving allocated treatment with reasons, number of patients with discontinued/completed treatment with reason, number of patients excluded from specific study populations with reason)
  - End of individual study participation (frequencies of reasons)
- Patient status at baseline and disease specific characteristics
  - Age, Body Mass Index (descriptive statistics)
  - Gender, ethnicity (frequencies)

- Performance Status: ECOG (frequencies)
- Time from primary diagnosis to acalabrutinib treatment (descriptive statistics)
- Presence of mutations, cytogenetic aberrations (including light chain expression) (frequencies)
- Bone marrow examination (frequencies for categories)
- Presence of lymphocytosis in bone marrow (frequencies)
- Rai stage (frequencies)
- CLL-IPI score (frequencies)
- CCI (frequencies)
- Creatinine clearance (frequencies for categories)
- Median leucocyte count (frequencies)
- Median lymphocyte count (frequencies)
- Thrombocytes ≤ / > 100.000/µl (frequencies)
- Hemoglobin ≤ / > 11.0 g/dl (frequencies)

- Medical history and concomitant diseases
  - Charlson comorbidities (frequencies)
- Other treatments during acalabrutinib therapy
  - Proportion of patients receiving radiotherapy (frequencies)
  - Proportion of patients with any surgery and location of surgery (frequencies)

- Adverse Events:

  An overview table will be provided displaying the incidence proportion and number of cases of any
  - TEAE
  - TEAE related to acalabrutinib
  - Serious TEAE
  - Non-serious TEAE
  - Serious TEAE related to acalabrutinib
  - Grade 1/2 TEAE
  - Grade 3/4 TEAE
  - Grade 3 TEAE
  - Grade 4 TEAE
  - Grade 3/4 TEAE related to acalabrutinib
  - Grade 3 TEAE related to acalabrutinib
  - Grade 4 TEAE related to acalabrutinib
  - TEAE leading to discontinuation of acalabrutinib
  - TEAE related to acalabrutinib leading to discontinuation of acalabrutinib
  - Fatal TEAE
  - Fatal TEAE related to acalabrutinib.

  Frequencies and percentages of MedDRA System Organ Classes and Preferred Terms will be presented for all
  - TEAE
  - Grade 1/2 TEAE
  - Grade 3/4 TEAE

- Fatal TEAE
- Serious TEAE
- TEAE related to acalabrutinib
- Grade 1/2 TEAE related to acalabrutinib
- Grade 3/4 TEAE related to acalabrutinib
- Fatal TEAE related to acalabrutinib
- Serious TEAE related to acalabrutinib

A by-patient listing of AE data will be provided, including all enrolled patients, those excluded from FAS will be flagged.

A detailed description of all planned analyses will be specified in the statistical analysis plan.

8. Quality Control and Data Management

8.1. Monitoring

Participating sites will be initiated by a webinar (web-based seminar).

The site will be informed about main objectives and procedures of the study as described in this observational plan. Initiation will include discussion of relevant issues i.e., patient inclusion, patient information, documentation of observed parameters, SAE reporting.

An interim visit will be performed at least once at each participating site by monitors authorized by iOMEDICO. The number of monitoring visits depends on the number of recruited patients at a site. Verification of collected data will be done by comparing the data in the patient file with the data documented in the eCRF (Source Data Verification). The extent of monitoring and the monitoring procedures are specified in a monitoring plan.

The monitor will discuss any issue with the treating physician or delegate. Adequate time for visit(s) should be provided. The treating physician has to ensure that the monitor has direct access (in accordance to the ICH GCP guidelines, Sections 4.9.7 and 6.10) to source documents which support data recorded in the eCRF, as defined in the ICH GCP guidelines, Sections 1.51 and 1.52. The treating physician agrees to cooperate with the study monitor to ensure that any problems detected during monitoring visits are resolved in a timely manner.

Additionally, a periodic centralized monitoring will be performed. Queries entered in the eCRF by the central monitor should be resolved and answered by the site in a timely manner. Inquiries or demands concerning documentation or conduct of the study might be clarified by telephone calls or e-mails between the treating physician/ site personnel and iOMEDICO.

8.2. Data Management

The data management for this study will be performed by iOMEDICO.

For electronic data capturing and data management of this study the web-based validated software (**io*study*** office edc 6) will be employed.

The eCRFs for data capturing includes online validation of CRFs during data capturing, e.g., check on range, plausibility. In addition to system-based plausibility checks, a formal query process will be implemented to solve inconsistencies in documented data.

The participating physician agrees to provide all necessary background information concerning his/her documentation on demand. The participating physician ensures that the documented information is captured correctly. The correctness and completeness of the data entries will be confirmed by electronic signature.

8.3. Site File and Archiving

The site will receive a site file upon study start. This file will contain all documents necessary for the conduct of the study and will be updated and completed throughout the study. It must be accessible for review by the monitor or for audit by iOMEDICO audit during and after the study.

All study documents, including the patient identification list and the signed patient informed consent forms must be safely maintained and archived for at least 10 years. If archiving is no longer possible at the site or the location of archiving is changing, the participating physician must inform iOMEDICO.

9. Administrative Requirements

9.1. Documentation

A project specific contract between study site and iOMEDICO is signed to confirm the participation of the physician and site.

An eCRF will be used for recording all data for each patient. It is the responsibility of the participating physician to ensure that the eCRF is properly completed. The eCRF must be completed for all patients who have signed the informed consent form. The eCRF has to be filled by the participating physician or a person designated and authorized by the physician.

The patient record serves as the patient's source documentation and should be maintained at the study site. All entries in the eCRF should be substantiated by entries in the original patient file. Patient names should not be documented in the eCRF or on any other documents which will be sent to iOMEDICO or the marketing authorization holder (MAH).

After the completion of a patient-specific eCRF, the participating physician or his delegated designee has to confirm the documented content by signing and dating the signature module on the last eCRF page using a specific password assigned by iOMEDICO (instructions are given in the eCRF). With his/her signature it is declared that all information recorded for a patient is complete and is accurate.

The software **io*study*** *office edc 6* is property of iOMEDICO and will be provided to the sites for the duration of the study. **io*study*** *office edc 6* was developed for data capturing purposes and has been adapted to this specific study. All the data collected during this study will be handled confidentially.

9.2. Management of Patient Questionnaires

The bleeding event questionnaire will be used to document if bleeding events occurred in-between visits in routine care. Patients will be asked at if distinct events occurred in the time between the last visit until the current visit and discuss the questionnaire with the physician to determine of any (S)AE occurred until end of acalabrutinib treatment.

The paper-based questionnaire will be distributed by study site to the patient at every visit in routine care until end of acalabrutinib treatment. For retrospectively included patients, the questionnaire will be additionally distributed at inclusion to evaluate bleeding events between start of acalabrutinib treatment and inclusion (Table 6).

The patient should be given the questionnaire(s) to be completed on the day of the scheduled visit before any clinical assessment. The center must provide a quiet place where the patient has sufficient time and can focus on the questions, without seeking advice from others.

The questionnaire should be used as a documentation aid for dialog with the treating physician to determine whether AE occurred that need to be transferred to the medical records and the eCRF.

The site personnel (referring to who could be responsible for administering of PROs) should inform the patients, not to add additional handwritten information on the questionnaires (unless explicitly stated). Furthermore, the physician should check the questionnaire for completeness and ask the patient to complete any missing

responses. This questionnaire will only be used as documentation aid and will not be transferred to the eCRF but is seen as source document. Distribution and fill-out date will be tracked in the eCRF.

Table 6. Distribution schedule of bleeding assessment tool.

Patients	Baseline	During acalabrutinib treatment
	After informed consent.	At each visit in routine care during treatment with acalabrutinib
Retrospectively included	X	X
Prospectively included		X

9.3. Ethical Considerations

According to local guidelines and Standard Operating Procedures (SOPs) of iOMEDICO, an Ethics Committee opinion will be sought for this study. The observational plan including the informed consent form, the patient questionnaire and further documents required by the Ethics Committee will be matter of the examination. An Ethics Committee opinion will also be sought for any amendment to the protocol in accordance with local requirements.

Supplementary, the participating physicians are free to submit the observational plan and material provided to the patients to their respective responsible Ethics Committee according to their legal professional obligation.

9.4. Notification to Competent Federal Authority and Relevant Associations

According to German Pharmaceutical Act § 67(6), this NIS will be submitted by iOMEDICO to the relevant central authority, the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM), the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung; NASHIP (KBV)), the Statutory Health Insurance Funds (Spitzenverband Bund der Krankenkassen), and the Association of Private Health Insurance Funds (Verband der privaten Krankenversicherung e.V.). All participating physicians, study sites as well as study timelines and objectives (observational plan) of the NIS will be notified to the NASHIP, the Statutory Health Insurance Funds, and the Association of Private Health Insurance Funds. The extent of remuneration is provided to NASHIP and the Statutory Health Insurance Funds, continuously during NIS conduction and at the EOS.

9.5. Patient Informed Consent

The treating physician is responsible for obtaining written informed consent from each patient participating in this study. The informed consent must be freely signed and personally dated by the patient and by the person who conducted the informed consent discussion before the beginning of the study. The patient receives a copy of the consent form. Date of signed informed consent will be documented in the eCRF and in the patient record.

When a patient withdraws from further participation and data collection within the study, the date of study completion and reason for study completion (informed consent withdrawal) should be documented in the eCRF and in the patient record. Further data collection should be stopped by the date of withdrawal. If a patient only withdraws consent to participate in one or more optional subprojects (e.g., participation in the data merging), the date of subproject withdrawal must be documented in the eCRF and the patient record. In this case, further data collection for the affected subproject only must be stopped, while data collection for the main study (and other subprojects not affected by the withdrawal) should continue.

9.6. Confidentiality / Patient Identification

The participating physician must assure that patients' pseudonymity will be strictly maintained and that their identities are protected from unauthorized parties. CRFs and other documents submitted to iOMEDICO must never

contain the name of a participating patient. All patients will be identified by a unique identifier which will be used on all CRFs and any other material submitted to iOMEDICO. It is the participating physician's responsibility that all medical records and sufficient information related to the identity of the patients will be retained. Personal medical records may be reviewed by representatives of iOMEDICO. They should have direct access to all requested study-related records. Every reasonable effort will be made to maintain such information as confidential.

The results of the study may be presented in reports, at scientific meetings or published in peer-reviewed scientific journals or online clinical trials registries; however, patient names will never be used in such reports, presentations or publications. Data will only be published at an aggregated anonymous level.

9.7. Remuneration and Reimbursement

Medication and medical treatment will be paid by cost bearers, such as statutory health insurance organizations or private insurances since the prescription and the choice of treatment is part of a routine clinical situation.

The treating physician's fee has to be conceived only as reimbursement of expenses regarding patient information, the documentation of the predefined clinical data, the reporting and monitoring activities and will be calculated based on the 'Gebührenordnung für Ärzte' (GoÄ). Only evaluable data with regard to this observational plan can be reimbursed.

10. Plans for Disseminating and Communicating Study Results

10.1. Publication Policy

The basic study design and relevant contact details regarding this NIS will be published in a public trial register (e.g., ClinicalTrials.gov) before enrollment of the first patient.

It is planned to publish a full paper in a peer-reviewed journal or online clinical trial registries not later than one year after finalization of the study report.

10.2. Study Report

A final study report will be prepared and provided to the applicable regulatory agencies. iOMEDICO will ensure that the report meets the standards set out in the Guideline on Good Pharmacoepidemiology Practices (GPP) and Good Pharmacovigilance Practices (GVP) Module VIII.

The final study report will be submitted within one year after LPO/LPLV.

11. Funding Source

This study is financially supported by Astra Zeneca.

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13. Appendices

13.1. Common Toxicity Criteria (CTC): Classification of Adverse Events During Therapy

The classification of AEs during therapy of this study is based on the National Cancer Institute 'Common Terminology Criteria for Adverse Events' (NCI CTCAE), version 5.0. For details, please refer to the homepage of the National Cancer Institute (NCI). The link can be found in the Site File.

13.2. MedDRA

AEs will be coded using the MedDRA version 25.0 during the study and the coding will be upgraded to the newest version for the final analysis.

13.3. Adverse events of special interest

The following events are adverse events of special interest (AESIs) for patients exposed to acalabrutinib:

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)

13.4. Performance Status

13.4.1. Karnofsky Performance Status

Score	Karnofsky Index
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of their personal needs
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

13.4.2. ECOG Performance Status

ECOG Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work

2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

13.4.3. Karnofsky-ECOG Conversion Table

Reference: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

ECOG Performance Status		Karnofsky Index (KI)	
0	Fully active, able to carry on all pre-disease performance without restriction	100%	Normal, no complaints
		90%	Able to carry on normal activities. Minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80%	Normal activity with effort
		70%	Care for self. Unable to carry on normal activity or to do active work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	60%	Requires occasional assistance, but able to care for most of his needs
		50%	Requires considerable assistance and frequent medical care
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	40%	Disabled. Requires special care and assistance
		30%	Severly disabled. Hospitalisation indicated though death nonimminent
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	20%	Very sick. Hospitalisation necessary. Active supportive treatment necessary
		10%	Moribund
0	Dead	0%	Dead

13.5. Patient questionnaire

English version

Reference: Rodeghiero et al. 2010, Tosetto et al. 2011, Fasulo et al. 2018

Bleeding event assessment tool – adapted according to the International society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH – BAT)

To be filled out by the patient		**To be filled out by the physician**
Fill-out date: ……..		Is the event a (serious) adverse event ((S)AE), which need to be documented in the electronic Case report Form (eCRF)?
Did you have epistaxis of any grade since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have bruising, subcutaneous hematomas, purpura or ecchymoses of any grade since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have prolonged bleeding from minor wounds since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have hematuria since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have gastrointestinal bleeding (hematemesis, melena, hematochezia) of any grade since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have oral bleeding (spontaneous bleeding, or after brushing/flossing, gum bleeding, bleeding after bites to lip & tongue) of any grade since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have heavy bleeding after tooth/teeth extraction of any grade since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have bleeding after surgery or major trauma of any grade since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have muscle hematomas or hemarthrosis since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Did you have any other bleeding since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No
Only to be filled out for female patients!		
Did you have unusual heavy menstrual bleeding since the last visit in routine care at your physician?	□ Yes □ No	□ Yes, an AE □ Yes, an SAE Onset date:…… □ No

German version

Instrument zur Bewertung von Blutungsereignissen – adaptiert gemäß dem Bleeding Assessment Tool der Internationalen Gesellschaft für Thrombose und Hämostase (ISTH - BAT)

Vom Patienten auszufüllen		**Vom Arzt auszufüllen**	
Ausfülldatum: ……..		Handelt es sich bei dem Ereignis um ein (schwerwiegendes) unerwünschtes Ereignis ((S)AE), das im eCRF dokumentiert werden muss?	
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt Nasenbluten egal wie schwerwiegend?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt Blutergüsse, subkutane Hämatome, Einblutungen in die Haut (Pünktchen oder Flächenförmig) egal wie schwerwiegend?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt anhaltende Blutungen bei kleineren Wunden/Verletzungen?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt Anzeichen von Blut im Urin (Hämaturie) egal wie schwerwiegend?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt gastrointestinale Blutungen (Erbrechen von Blut, Blut im Stuhl (dunkel- oder hellroter Stuhl) egal wie schwerwiegend?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt Blutungen im Mund (spontane Blutungen oder Blutungen nach dem Zähneputzen/der Zahnseide, Zahnfleischbluten, Blutungen nach Bissen auf Lippe und Zunge) egal wie schwerwiegend?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt starke Blutungen nach einer oder mehreren Zahnextraktionen?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt Blutungen nach einer Operation oder einer schweren Verletzung egal wie schwerwiegend?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt Muskelhämatome oder Blutungen in den Gelenken?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt weitere Blutungen?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE
Nur von weiblichen Patientinnen auszufüllen!			
Hatten Sie seit dem letzten Besuch bei Ihrem Arzt ungewöhnlich starke Menstruationsblutungen (Monatsblutungen)?	□ Ja □ Nein	□ Ja, ein AE Beginndatum □ Nein	□ Ja, ein SAE

13.6. Physician questionnaire

English version

Treatment decision questionnaire – Reasons for treatment decision					
	Applies not at all	Applies less	Applies partly	Applies quite	Applies completely
Efficacy					
Fast tumor response					
Profile of side effects					
Profile of side effects of other treatment options					
Type of application					
Frequency of application					
Previous experience					
Guideline recommendations					
Tumor board decision					
Price					
Travel distance to the physician' s practice					
Maintenance of quality of life					
Compatibility of therapy and work					
Age					
Comorbidities					
Anticipated patient's compliance					
Patient wish					

German version

Fragebogen zur Behandlungsentscheidung - Gründe für die Behandlungsentscheidung					
	Trifft überhaupt nicht zu	Trifft weniger zu	Trifft teilweise zu	Trifft ziemlich zu	Trifft vollständig zu
Wirksamkeit					
Schnelles Ansprechen des Tumors					
Nebenwirkungsprofil					
Nebenwirkungsprofil anderer Therapieoptionen					
Applikationsart					
Applikationsfrequenz					
Bisherige Erfahrungen					
Empfehlung der Leitlinie					
Entscheidung des Tumorboards					
Kosten					
Entfernung zur Arztpraxis					
Aufrechterhaltung der Lebensqualität					

Vereinbarkeit von Therapie und Beruf
Alter
Komorbiditäten
Erwartete Compliance des Patienten
Wunsch des Patienten