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COVID-19 Infection in Patients With Chronic Lymphocytic Leukemia Receiving Acalabrutinib in the Phase 3B ASSURE Study

Carsten U. Niemann[1], Farrukh T. Awan[2], Laura Fogliatto[3], Eugene Nikitin[4], Olga Samoilova[5], Adel Habib[6], Kayhan Foroutanpour[6], Nataliya Kuptsova-Clarkson[6], Stephen Opat[7]

Correspondence: Carsten U. Niemann (carsten.utoft.niemann@regionh.dk).

Chronic lymphocytic leukemia (CLL) is associated with defects in cellular and humoral immunity, resulting in an increased risk of infection.[1] Therefore, patients with CLL may be more susceptible to more severe COVID-19 infection.[2] ASSURE is an ongoing global, phase 3b study (NCT04008706) designed to evaluate the safety and efficacy of acalabrutinib, a highly selective, next-generation covalent Bruton tyrosine kinase inhibitor (BTKi), in patients with CLL. Previous data have indicated that treatment with a BTKi may impair the antibody response to vaccination, but data on safety outcomes from COVID-19 infection while on BTKis are ambiguous.[2,3] The timing of a planned safety interim analysis of ASSURE presented an opportunity to review data for patients who developed COVID-19 while on study. Here, we report characteristics and outcomes of COVID-19–infected patients from the trial. Our descriptive analysis revealed that respiratory disorders at baseline and relapsed/refractory (R/R) CLL were more frequent characteristics among patients with CLL who died due to COVID-19 infection. Pre-existing hypertension and treatment with antivirals for COVID-19 were more frequent among those who survived the COVID-19 infection. No pattern emerged with regard to survival or death from COVID-19 when examining continued dosing of acalabrutinib or dose interruptions at the time of COVID-19 infection.

[1]Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
[3]Hospital de Clinicas de Porte Alegre, Porte Alegre, Brazil
[4]S.P. Botkin's City Hospital, Moscow, Russian Federation
[5]Regional Clinical Hospital, Nizhny Novgorod, Russian Federation
[6]AstraZeneca, Gaithersburg, MD, USA
[7]Haematology Department, Monash Health, School of Clinical Sciences, Monash University, Melbourne, Australia
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ASSURE is an international, multicenter, open-label, single-arm study. Patients were adults ≥18 years with symptomatic/active CLL per International Workshop on Chronic Lymphocytic Leukemia guidelines[4] and Eastern Cooperative Oncology Group performance status ≤2. Patients were excluded if they previously had disease progression while on a BTKi. Patients were enrolled into 1 of 3 cohorts: treatment naive (TN), R/R, or prior BTKi therapy (discontinued BTKi for any reason except disease progression). All patients will receive acalabrutinib 100 mg twice daily until completion of 48 cycles (28 days/cycle), disease progression, death, or intolerability.

This report (based on a planned interim analysis) includes only the subset of patients with known or suspected COVID-19 infection during the study, defined as having an adverse event occurring during the pandemic timeframe (ie, after March 11, 2020) with a preferred term within the adverse event search criteria developed by the latest MedDRA MSSO guidance for COVID-19. SARS-CoV-2 test results were not collected. Among COVID-19–infected patients, patient characteristics, treatment disruptions or discontinuations, relevant comorbidities (comorbidities that increase risk of severe COVID-19 or worse outcomes with COVID-19, such as hypertension, respiratory diseases, cardiovascular disease, obesity, and diabetes[5–8]), concomitant medications (including treatments for COVID-19), COVID-19 vaccination status, prior chemotherapy treatments (used by >20% of patients), and patient outcomes are reported descriptively. Characteristics were also stratified by outcome of COVID-19 infection in terms of survival (including those who died from causes unrelated to COVID-19).

At the time of this analysis (data cutoff: August 10, 2021), 545 patients were enrolled and 189 (35%) had received at least 1 dose of vaccination for COVID-19, reflecting the vaccination coverage of the countries participating in the trial. Confirmed or suspected COVID-19 infection occurred in 67 patients (12%) (**Table 1**). Among the 67 patients with COVID-19 infection, median age was 69 years (range, 43–90), 61% were male, and 88% were White. For COVID-19–infected patients, 42% (n = 28) had TN CLL and 57% (n = 38) had R/R disease status prior to acalabrutinib, and 1 patient previously received a BTKi. Neutropenia was reported in 9% of the 67 COVID-19–infected patients. No patient had lymphopenia. In total, 20 of the 67 patients (30%) died due to COVID-19 infection. Of the 67 patients, 47 (70%) survived or died from causes that were not attributed to COVID-19. The 4 patients who died of causes deemed unrelated to COVID-19 included 3 patients who died ≥15 days after COVID-19 resolution (reasons included

Table 1.

Comorbidities and COVID-19 Outcomes for Patients With COVID-19 Infection[a]

	Survived COVID-19 (n = 47[b])	Fatal COVID-19 (n = 20[c])
Baseline characteristics		
Age, years, median (range)	69 (43, 90)	69 (52, 84)
Treatment naive (n = 28), n (%)	21 (45)	7 (35)
Relapsed/refractory (n = 38), n (%)	26 (55)	12 (60)
Prior BTKi treatment (n = 1), n (%)	0	1 (5)
Time from acalabrutinib start to COVID-19 infection, days, median (range)	177 (–30[d], 449)	181 (10, 484)
Time from acalabrutinib start to COVID-19 infection in treatment-naive patients	128 (38, 390)	193 (68, 254)
Time from acalabrutinib start to COVID-19 infection in relapsed/refractory patients	195 (–30[d], 449)	131 (10, 484)
Relevant comorbidities, n (%)		
Hypertension (n = 42)	34 (72)	8 (40)
Cardiac disorders (n = 19)	14 (30)	5 (25)
Vascular disorders (other than hypertension) (n = 18)	14 (30)	4 (20)
Respiratory disorders (n = 16)	9 (19)	7 (35)
Diabetes mellitus (n = 12)	8 (17)	4 (20)
Obesity (n = 7)	5 (11)	2 (10)
Most common prior therapies for CLL, n (%)[e]		
Purine analogs (n = 21)	15 (32)	6 (30)
Anti-CD20 antibodies (n = 36)	24 (51)	12 (60)
Alkylating agents (n = 35)	24 (51)	11 (55)
Serious adverse event (COVID-19)[f]	35 (74)	19 (95)[g]
Medications used to treat COVID-19, n (%)		
Corticosteroids		
Dexamethasone (n = 22)	15 (32)	7 (35)
Methylprednisolone (n = 2)	1 (2)	1 (5)
Prednisolone/prednisone (n=2)	2 (4)	0
Antivirals	14 (30)	3 (15)
Antivirals with activity against COVID-19		
Favipiravir (n = 8)	6 (13)	2 (10)
Remdesivir (n = 6)	6 (13)	0
Respiratory-related antivirals		
Umifenovir (n = 2)	1 (2)	1 (5)
Oseltamivir (n = 2)	2 (4)	0
Ribavirin (n = 1)	0	1 (5)
Other antivirals		
Lopinavir + ritonavir (n = 1)	0	1 (5)
Patients treated with only 1 antiviral	13 (28)	1 (5)
Patients treated with 2+ antivirals	1 (2)	2 (10)
Baricitinib (n = 2)	1 (2)	1 (5)
Biologics	10 (21)	4 (20)
Tocilizumab (n = 9)	6 (13)	3 (15)
Olokizumab (n = 3)	2 (4)	1 (5)
Fresh frozen plasma (n = 2)	1 (2)	1 (5)
COVID-19 convalescent plasma (n = 2)	2 (4)	0
Interferon alfa (n = 2)	2 (4)	0
Interferon beta-1b (n = 1)	0	1 (5)
Sarilumab (n = 1)	1 (2)	0

[a]Includes outcomes for the preferred term events of COVID-19, suspected COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive, and post-acute COVID-19 syndrome.
[b]Four patients died from causes unrelated to COVID-19.
[c]One patient's outcome was unclear at time of data cutoff; however, the patient died after the data cutoff.
[d]One patient was diagnosed with COVID-19 prior to study enrollment.
[e]Other previously used treatments included vinca alkaloids (n = 13), anthracyclines (n = 6), venetoclax (n = 1), radiotherapy (n = 1), anti-CD23 antibody (n = 1), platinum agents (n = 1), topoisomerase inhibitor (n = 1), and pyrimidine analog (n = 1).
[f]A serious adverse event was defined as an event that either results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the aforementioned outcomes.
[g]COVID-19 adverse event for 1 additional patient was reported as not serious at the time of data cutoff; however, this patient subsequently died due to pneumonia following COVID-19 infection.
BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia.

lung adenocarcinoma, aortic coarctation, and septic shock lung focus in 1 patient each) and 1 patient who died during their COVID-19 infection (meningoencephalitis). An analysis of characteristics of COVID-19 survivors and those who died from causes unrelated to COVID-19 is provided in Suppl. Table S1. There was a higher prevalence of R/R CLL than TN CLL among patients with a fatal COVID-19 outcome (**Table 1**).

COVID-19 infection resulted in at least 1 skipped or postponed study visit for 15% (n = 10) and discontinuation of acalabrutinib treatment in 31% (n = 21) of COVID-19–infected patients. Twenty-six (39%) of the 67 patients with COVID-19 infection had an acalabrutinib dose interruption during their infection. Among the 47 patients who did not die from COVID-19, 43% (n = 20) had a dose interruption during the infection; 1 of these patients had a dose interruption, resumed treatment, and discontinued treatment prior to end of infection, and another patient had a dose interruption, discontinued treatment, and died after resolution of infection (**Figure 1**). Among the 47 patients who did not die from COVID-19 and did not have a dose interruption, 1 patient discontinued treatment during COVID-19 infection, a second patient discontinued treatment prior to the infection occurring, and a third patient had an infection that was resolved prior to starting acalabrutinib treatment.

Among the 20 patients who died from COVID-19, 80% (n = 16) discontinued treatment and/or had a dose interruption prior to death from COVID-19 (**Figure 1**). The median (range) time from last dose of acalabrutinib to death among these 16 patients was 10.5 (range, 1–137) days.

Among the 67 patients with confirmed or suspected COVID-19 infection, a medical history of hypertension was reported in 63%, respiratory disease in 24%, cardiac disease in 28% (most common: angina pectoris [8%], coronary artery disease [8%], and myocardial ischemia [6%]), diabetes in 18%, and obesity in 10% of patients. History of respiratory disorders occurred more frequently in patients who died from COVID-19 (35%) than in those who did not die from COVID-19 (19%). Conversely, pre-existing hypertension was more prevalent in those who did not die from COVID-19 (72%) than in those who died from COVID-19 (40%) (**Table 1**; Suppl. Figure S1A; Suppl. Table S1). The total number of specific comorbidities was not associated with COVID-19–related death; however, patient numbers were small (Suppl. Figure S1B).

Antiviral medications appeared more frequently during the COVID-19 infection period among patients who did not die from COVID-19 infection. Among the 3 most frequent previous CLL therapies, there was a trend for higher frequency of prior CD20 monoclonal antibodies among patients dying from COVID-19 (**Table 1**; Suppl. Table S1). No patients received anti–COVID-19 monoclonal antibodies and only 2 patients received COVID-19 convalescent plasma. The most common concomitant medications used before, during, or after COVID-19 infection are provided in Suppl. Table S2.

The majority of infected patients (n = 66/67; 99%) were not vaccinated at the time of COVID-19 infection. Only 1 patient received 1 dose of COVID-19 vaccine before becoming infected; this patient died from infection without receiving a second dose. Eleven other patients received at least 1 dose of COVID-19 vaccine but only after recovering from COVID-19 infection.

Limitations of this analysis include the small sample size of COVID-19–infected patients. Results of this analysis are primarily descriptive and differences were not tested for statistical significance. In addition, the ASSURE trial was not designed to assess the course of COVID-19 infections and did not include a control group to assess differences in COVID-19–related outcomes for patients who did or did not receive acalabrutinib. COVID-19 infection in these patients occurred between April 2020 and August 2021 (data cutoff); therefore, different COVID-19 variants were in circulation (eg, delta) over time, and variant disease severity may have influenced the infection

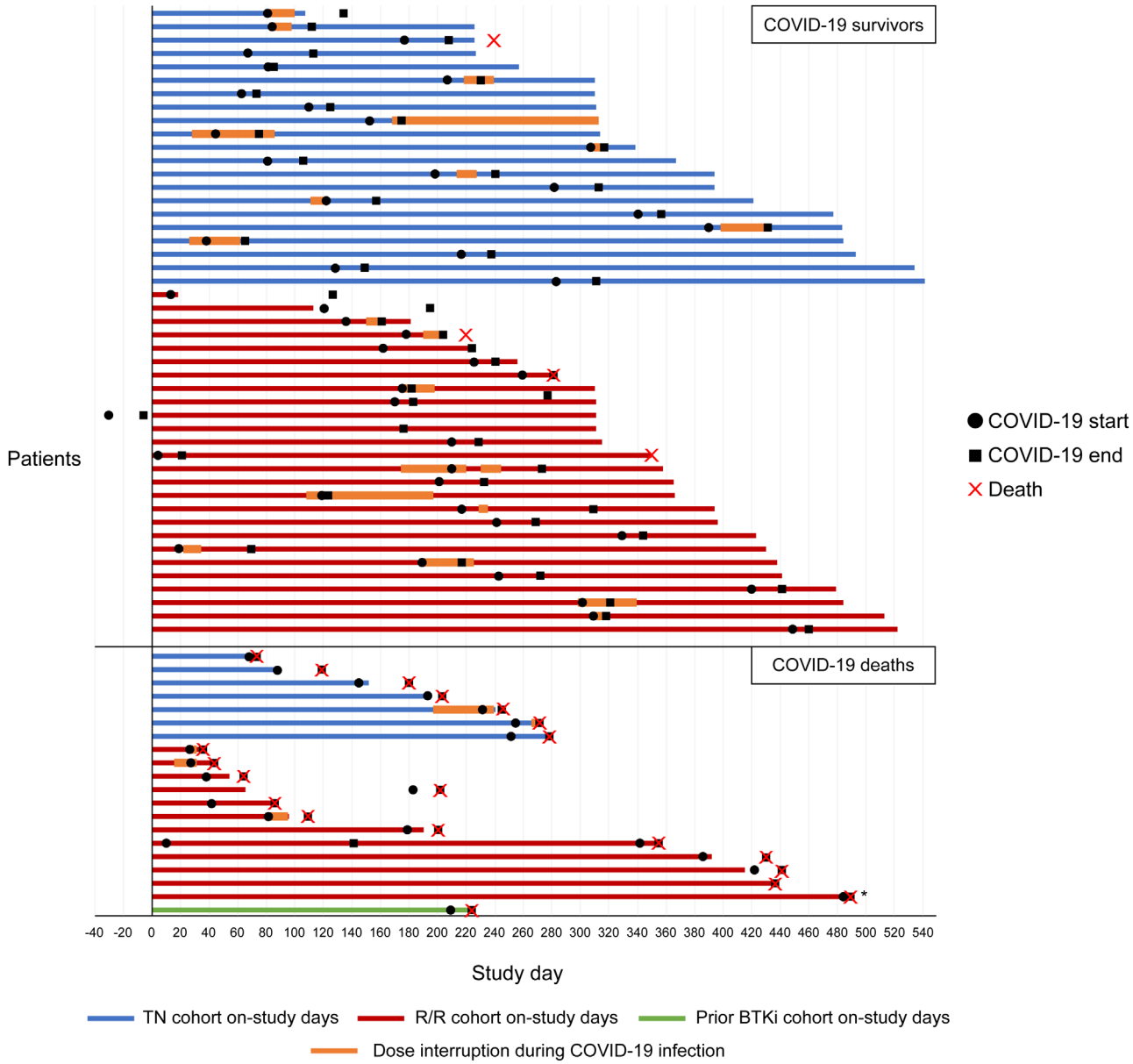

Figure 1. Patient timeline of on-study acalabrutinib treatment, COVID-19 infection, outcome, and acalabrutinib dose interruptions during COVID-19 infection. Only dose interruptions that occurred during COVID-19 infection are included. Deaths considered unrelated to COVID-19 among COVID-19 survivors were reported in 4 patients and were due to lung adenocarcinoma, aortic coarctation, meningoencephalitis, and septic shock lung focus (1 patient each). *Patient treatment and infection duration reflects data at time of data cutoff; death from COVID-19 occurred after the data cutoff. BTKi = Bruton tyrosine kinase inhibitor; R/R = relapse/refractory; TN = treatment naive.

outcomes. Data on COVID-19 variants in infected patients were not collected in this study. Details on which COVID-19 vaccination patients received were not consistently collected for all enrolled patients, thus the impact of particular COVID-19 vaccinations on outcomes was not assessed. All but one patient among those who were infected received vaccination after the infection. Data on hospital and intensive care unit admission rates, persistence, and readmission for COVID-19 were not collected. The ASSURE study protocol has since been amended to recommend COVID-19 vaccination and includes guidance for monitoring and acalabrutinib treatment during COVID-19 infection.

In this interim analysis of patients with CLL treated with acalabrutinib in the ASSURE trial, approximately 12% of participants were infected with COVID-19, among whom approximately 30% died from infection. This mortality rate is similar to that observed in COVID-19–infected CLL patients in prior retrospective studies (~29%).[2,9,10] Prior data have suggested that patients on BTKis may have an impaired antibody response to COVID-19 infection[11]; however, the current study indicates that the clinical outcome upon COVID-19 infection during treatment with the BTKi acalabrutinib is similar to that reported for patients with CLL who have COVID-19, regardless of CLL treatment.[10] These reports have also indicated that BTKis do not have significant impact on mortality.[10] Furthermore, history of respiratory disorders and R/R CLL were more frequent among those who died, whereas pre-existing hypertension was more frequent among survivors. Hypertension is well recognized as a risk factor for severe COVID-19.[12–14] The outcome of COVID-19 infection while using different antihypertensive medications

is less clear, although some data may support a benefit.[15] It is possible that in the setting of a clinical trial, pre-existing hypertension may be better monitored and controlled than in real-world settings; however, assessing compliance with hypertensive medication was beyond the scope of the current trial, and other unknown factors may be influencing the results observed here. A slightly higher frequency of prior anti-CD20 monoclonal antibody treatment was observed for patients with a fatal outcome. In the literature, COVID-19–infected patients treated with these agents are at higher risk of mortality.[16] However, the number of patients receiving anti-CD20 treatment was very small in the current analysis, and the proximity of this treatment to COVID-19 infection varied from months to several years (median time from last dose of anti-CD20 treatment to COVID-19 infection was approximately 27 months [range, 6 months to 15 years]). Five patients received their last dose of anti-CD20 treatment within 12 months of infection, 3 of whom died from the infection and 1 who died from meningoencephalitis. Patients treated with antivirals during the COVID-19 infection were more likely to recover, and no difference in mortality outcome for patients using systemic steroids was detected in the current analysis, similar to published reports of corticosteroid use in patients with lymphoma infected with COVID-19.[17] This analysis supports the use of antiviral therapy upon COVID-19 infection in patients with CLL, regardless of the concurrent use of BTKis, and reinforces the need for close monitoring of patients with prior respiratory disease and those who have more advanced or heavily pretreated CLL.

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AUTHOR CONTRIBUTIONS

CUN, FTA, KF, and SO designed the study. CUN, FTA, LF, EN, OS, and SO served as study investigators. CUN, FTA, LF, EN, OS, and SO enrolled patients. CUN, FTA, AH, KF, NKC, and SO analyzed the study data. All authors interpreted the study data, prepared the article, performed article review and revisions, and provided final approval of the manuscript.

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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