Supplemental Digital Content

SDC, Table 1. Subsequent anticancer therapies[a]

	Acalabrutinib (n=155)	IdR/BR (n=155)	Total (n=310)
Number of subsequent anticancer therapies, n (%)			
1	27 (17.4)	29 (18.7)	56 (18.1)
2	8 (5.2)	5 (3.2)	13 (4.2)
3	1 (0.6)	2 (1.3)	3 (1.0)
≥4	2 (1.3)	0	2 (0.6)
Median	1	1	1
Range	1–4	1–3	1–4
Subsequent anticancer therapy category,[b] n (%)			
Acalabrutinib	1 (0.6)	1 (0.6)	2 (0.6)
Alkylators other than bendamustine	11 (7.1)	12 (7.7)	23 (7.4)
Anti-CD20 monoclonal antibody	14 (9.0)	10 (6.5)	24 (7.7)
Bendamustine	2 (1.3)	3 (1.9)	5 (1.6)
Bleomycin	0	1 (0.6)	1 (0.3)
Doxorubicin	5 (3.2)	7 (4.5)	12 (3.9)
Etoposide	2 (1.3)	1 (0.6)	3 (1.0)

Ibrutinib	6 (3.9)	7 (4.5)	13 (4.2)
Mitoxantrone	1 (0.6)	0	1 (0.3)
Other BTKi	3 (1.9)	1 (0.6)	4 (1.3)
Platinum-based regimens	2 (1.3)	1 (0.6)	3 (1.0)
Purine analogues	2 (1.3)	1 (0.6)	3 (1.0)
Rituximab	14 (9.0)	11 (7.1)	25 (8.1)
Steroids	9 (5.8)	7 (4.5)	16 (5.2)
Venetoclax	16 (10.3)	14 (9.0)	30 (9.7)
Vinca and other alkaloids	6 (3.9)	6 (3.9)	12 (3.9)
Other	3 (1.9)	1 (0.6)	4 (1.3)

[a]Based on main study period + crossover study period.

[b]Three subjects received subsequent therapy for non-CLL malignancies of myelodysplastic syndrome/acute myeloid leukemia (1 subject received azacitidine and cytarabine + idarubicin) and lung cancer (1 subject received cisplatin + vinorelbine and 1 subject received carboplatin + etoposide).

BTKi, Bruton tyrosine kinase inhibitor; BR, bendamustine plus rituximab; IdR, idelalisib plus rituximab.

SDC, Table 2. TEAEs of any grade leading to treatment discontinuation

TEAEs, n (%)	Acalabrutinib (n=154)	IdR (n=118)		BR (n=35)	
		Id	R	B	R
Patients with ≥1 TEAE leading to study drug discontinuation	36 (23.4)	76 (64.4)	16 (13.6)	4 (11.4)	6 (17.1)
COVID-19 pneumonia	3 (1.9)	0	0	0	0
Metastatic squamous cell carcinoma	2 (1.3)	0	0	0	0
Pneumonia	2 (1.3)	4 (3.4)	3 (2.5)	0	0
Squamous cell carcinoma of skin	2 (1.3)	0	0	0	0
Abdominal pain	1 (0.6)	0	0	0	0
Alanine aminotransferase increased	1 (0.6)	4 (3.4)	0	0	0
Anemia of malignant disease	1 (0.6)	0	0	0	0
Aortic aneurysm	1 (0.6)	0	0	0	0
Bladder transitional cell carcinoma	1 (0.6)	0	0	0	0
Brain abscess	1 (0.6)	0	0	0	0

Brain neoplasm	1 (0.6)	0	0	0	0
Brain neoplasm malignant	1 (0.6)	0	0	0	0
Bronchitis	1 (0.6)	0	0	1 (2.9)	1 (2.9)
Cardiac failure congestive	1 (0.6)	0	0	0	0
Cytopenia	1 (0.6)	0	0	0	0
Dehydration	1 (0.6)	0	0	0	0
Hematuria	1 (0.6)	0	0	0	0
Headache	1 (0.6)	0	0	0	0
Hemiparesis	1 (0.6)	0	0	0	0
Hepatitis B	1 (0.6)	0	0	0	0
Hepatitis C	1 (0.6)	0	0	0	0
Immune thrombocytopenia	1 (0.6)	0	0	0	0
Lung neoplasm malignant	1 (0.6)	0	0	0	0
Nasopharyngeal cancer	1 (0.6)	0	0	0	0
Neutropenia	1 (0.6)	1 (0.8)	0	0	0
Peritonitis	1 (0.6)	0	0	0	0
Prostate cancer	1 (0.6)	0	0	0	0
Pulmonary mass	1 (0.6)	0	0	0	0
Rash muscular	1 (0.6)	0	0	0	0

Respiratory failure	1 (0.6)	0	0	0	0
Respiratory tract infection	1 (0.6)	0	0	0	0
Sudden death, not otherwise specified	1 (0.6)	0	0	0	0
Diarrhea	0	19 (16.1)	0	0	0
Colitis	0	5 (4.2)	0	0	0
Pneumonitis	0	4 (3.4)	1 (0.8)	0	0
Transaminases increased	0	4 (3.4)	1 (0.8)	0	0
Aspartate aminotransferase increased	0	3 (2.5)	0	0	0
Interstitial lung disease	0	3 (2.5)	1 (0.8)	0	1 (2.9)
Hepatotoxicity	0	2 (1.7)	0	0	0
Neutrophil count decreased	0	2 (1.7)	0	0	0
Rash maculopapular	0	2 (1.7)	1 (0.8)	0	0
Thrombocytopenia	0	2 (1.7)	0	0	0
COVID-19	0	1 (0.8)	0	0	0
Cardiac failure chronic	0	1 (0.8)	1 (0.8)	0	0
Cardiopulmonary failure	0	1 (0.8)	0	0	0
Cytomegalovirus infection reactivation	0	1 (0.8)	0	0	0

Dyspepsia	0	1 (0.8)	0	0	0
Dyspnea	0	1 (0.8)	0	0	0
Enterocolitis	0	1 (0.8)	0	0	0
Epstein-Barr virus–positive mucocutaneous ulcer	0	1 (0.8)	0	0	0
Esophagitis	0	1 (0.8)	0	0	0
Hepatic cytolysis	0	1 (0.8)	0	0	0
Hepatic enzyme increased	0	1 (0.8)	0	0	0
Hepatitis B DNA assay positive	0	1 (0.8)	0	0	0
Hepatitis E	0	1 (0.8)	0	0	0
Liver injury	0	1 (0.8)	0	0	0
Myocardial infection	0	1 (0.8)	0	0	0
Pain in extremity	0	1 (0.8)	1 (0.8)	0	0
Pneumocystis jirovecii pneumonia	0	1 (0.8)	0	0	0
Pneumonia legionella	0	1 (0.8)	1 (0.8)	0	0
Pneumonia pneumococcal	0	1 (0.8)	0	0	0
Pruritus	0	1 (0.8)	0	0	0

Sepsis	0	1 (0.8)	0	0	0
Septic shock	0	1 (0.8)	1 (0.8)	0	0
Urinary tract infection	0	1 (0.8)	0	0	0
Vertigo	0	1 (0.8)	1 (0.8)	0	0
Gastroenteritis	0	0	1 (0.8)	0	0
Infusion-related reaction	0	0	1 (0.8)	0	0
Organizing pneumonia	0	0	1 (0.8)	0	0
Rash pustular	0	0	1 (0.8)	0	0
Urosepsis	0	0	1 (0.8)	0	0
Adenocarcinoma gastric	0	0	0	1 (2.9)	1 (2.9)
Hemolytic anemia	0	0	0	1 (2.9)	0
Cardiac failure acute	0	0	0	0	1 (2.9)
Hepatitis B reactivation	0	0	0	1 (2.9)	1 (2.9)
Urticaria	0	0	0	0	1 (2.9)

AEs were graded according to the Common Toxicity Criteria of the National Cancer Institute, version 4.03 and reported until 30 days after the last dose of study drug or at documented disease progression, whichever was longer. Data for AEs leading to treatment discontinuation were captured from the AE case report form.

AE, adverse event; B, bendamustine; BR, bendamustine plus rituximab; Id, idelalisib; IdR, idelalisib plus rituximab; R, rituximab; TEAE, treatment-emergent adverse event.

SDC Table 3. Outcomes in patients who discontinued treatment

	Discontinued due to AEs		Discontinued due to PD	
	Acala (n=36)	**IdR/BR (n=85)**	**Acala (n=34)**	**IdR/BR (n=26)**
Events, n (%)	28 (78)	67 (79)	30 (88)	26 (100)
Death	19 (53)	15 (18)	3 (9)	0
Start of crossover therapy	0	41 (48)	0	24 (92)
Start of subsequent anticancer therapy	9 (25)	11 (13)	27 (79)	2 (8)
Censored, n (%)	8 (22)	18 (21)	4 (12)	0
Alive and no crossover/subsequent anticancer therapy	8 (22)	18 (21)	4 (12)	0
Median TTNT, mo (range)	21.2 (2−NR)	17.7 (0.8−NR)	28.6 (2.1−NR)	15.8 (4.2−46.6)
HR (95% CI)	0.66 (0.40, 1.10)		0.43 (0.23, 0.79)	
P-value	0.1067		0.0052	

AE, adverse event; BR, bendamustine plus rituximab; CI, confidence interval; HR, hazard ratio; IdR, idelalisib plus rituximab; NR, not reached; PD, progressive disease; TTNT, time to next treatment.

SDC, Table 4. Summary of treatment-emergent grade ≥3 infections

Type of Infection, n (%)	Acalabrutinib (n=154)	IdR (n=118)	BR (n=35)
Pneumonia, upper respiratory, and respiratory			
Upper respiratory tract infection	3 (1.9)	4 (3.4)	1 (2.9)
Pneumonia	15 (9.7)	12 (10.2)	1 (2.9)
Respiratory tract infection	2 (1.3)	2 (1.7)	0
Bronchitis	2 (1.3)	1 (0.8)	1 (2.9)
Bronchitis pneumococcal	0	1 (0.8)	0
Infective exacerbation of bronchiectasis	0	1 (0.8)	0
Influenza	1 (0.6)	2 (1.7)	1 (2.9)
Pneumonia pneumococcal	0	5 (4.2)	0
Pneumonia legionella	0	1 (0.8)	0
Pneumonia pseudomonal	0	1 (0.8)	0
Pneumonia hemophilus	0	1 (0.8)	0
Pneumonia klebsiella	1 (0.6)	0	0
Lower respiratory tract infection	0	2 (1.7)	0
COVID-19	3 (1.9)	1 (0.8)	0
COVID-19 pneumonia	6 (3.9)	1 (0.8)	0
Fungal infections			

Pneumonia fungal	1 (0.6)	0	0
Pneumocystis jirovecii pneumonia	1 (0.6)	1 (0.8)	0
Sepsis			
Sepsis	1 (0.6)	1 (0.8)	0
Pseudomonal sepsis	1 (0.6)	1 (0.8)	0
Septic shock	0	1 (0.8)	0
Gastrointestinal			
Gastroenteritis	1 (0.6)	1 (0.8)	0
Clostridium difficile colitis	0	1 (0.8)	0
Gastroenteritis viral	0	0	1 (2.9)
Kidney and bladder			
Urinary tract infection	3 (1.9)	2 (1.7)	0
Escherichia urinary tract infection	1 (0.6)	1 (0.8)	0
Escherichia sepsis	1 (0.6)	0	0
Urosepsis	0	1 (0.8)	
Eye, ear and mouth			
Otitis media	1 (0.6)	0	0
Ophthalmic herpes zoster	1 (0.6)	0	0
Other			
Sinusitis	2 (1.3)	0	0

Cytomegalovirus infection	0	1 (0.8)	0
Cytomegalovirus infection reactivation	0	1 (0.8)	0
Cytomegalovirus viremia	0	1 (0.8)	0
Hemophilus infection	0	1 (0.8)	0
Epididymitis	1 (0.6)	0	0
Infection	0	1 (0.8)	0
Encephalitis viral	0	1 (0.8)	0
Herpes zoster	1 (0.6)	3 (2.5)	0
Hepatitis E	0	1 (0.8)	0
Herpes zoster reactivation	1 (0.6)	0	0
Herpes dermatitis	0	1 (0.8)	0
Pseudomonas infection	0	1 (0.8)	0
Peritonitis	1 (0.6)	0	0
Cellulitis	1 (0.6)	0	0
Diverticulitis	1 (0.6)	0	0
Epstein-Barr virus infection reactivation	1 (0.6)	0	0
Hepatitis B	1 (0.6)	0	0
Device-related infection	1 (0.6)	0	0
Postoperative wound infection	1 (0.6)	0	0
Appendicitis	1 (0.6)	0	0

Brain abscess	1 (0.6)	0	0

BR, bendamustine plus rituximab; IdR, idelalisib plus rituximab.

SDC, Table 5. TEAEs with a fatal outcome (grade 5)

TEAE, n (%)	Acalabrutinib (n=154)	IdR (n=118)	BR (n=35)
Subjects with ≥1 fatal TEAE	16 (10.4)	9 (7.6)	2 (5.7)
Brain neoplasm	1 (0.6)	0	0
Brain neoplasm malignant	1 (0.6)	0	0
Bronchitis	1 (0.6)	0	0
COVID-19	1 (0.6)	1 (0.8)	0
COVID-19 pneumonia	1 (0.6)	0	0
Cachexia	1 (0.6)	0	0
Cardiorespiratory arrest	1 (0.6)	0	0
Cardiopulmonary failure	1 (0.6)	2 (1.7)	0
Cerebral ischemia	1 (0.6)	0	0
Lung neoplasm malignant	1 (0.6)	0	0
Nasopharyngeal cancer	1 (0.6)	0	0
Neuroendocrine carcinoma	1 (0.6)	0	0
Pneumonia	1 (0.6)	0	0
Respiratory failure	1 (0.6)	0	0
Sepsis	1 (0.6)	1 (0.8)	0
Sudden death, not otherwise specified	1 (0.6)	0	0

Adenocarcinoma gastric	0	0	1 (2.9)
Cardiac failure acute	0	0	1 (2.9)
Cardiac failure chronic	0	1 (0.8)	0
Interstitial lung disease	0	1 (0.8)	0
Myocardial infarction	0	1 (0.8)	0
Pneumonia pseudomonal	0	1 (0.8)	0
Pneumonitis	0	1 (0.8)	0

AEs were graded according to the Common Toxicity Criteria of the National Cancer Institute, version 4.03 and reported until 30 days after the last dose of study drug or at documented disease progression, whichever was longer.

BR, bendamustine plus rituximab; IdR, idelalisib plus rituximab; TEAE, treatment-emergent adverse event.

SDC, Plain Language Summary

Why was this study done?

Until recently, the standard-of-care treatment for chronic lymphocytic leukemia (CLL) was chemoimmunotherapy, which combines immune-based treatments with traditional chemotherapy and is often toxic to the patient. Acalabrutinib is a newer oral therapy that selectively inhibits a protein called Bruton tyrosine kinase (BTK), which plays a role in worsening of disease in patients with CLL. ASCEND is a phase 3 study in patients with CLL who either relapsed after or stopped responding to previous treatments. It showed that after monitoring patients on treatment for 16.1 months, as well as after ~3 years, acalabrutinib treatment alone (monotherapy) yielded better responses and was safer compared with combination therapy with either chemoimmunotherapy or a nonchemotherapy-based drug combination. Here, we report the results of the ASCEND study after ~4 years of treatment.

How were the data collected?

Response to treatment (efficacy) and symptoms related to treatment (safety) were collected for a group of patients receiving only acalabrutinib and compared with two other patient groups. The two other patient groups received combination therapies, either chemoimmunotherapy (bendamustine plus rituximab) or a nonchemotherapy-based combination (idelalisib plus rituximab).

What were the results?

After ~4 years of treatment, more patients who were treated with acalabrutinib survived longer without worsening (progression) of disease compared with the combination regimens. After ~4 years of treatment, patients treated with acalabrutinib continued to have good responses and good overall survival, and the drug safety profile was sustained.

Why do the results matter to patients and physicians?

These results confirm that long-term acalabrutinib treatment as a chemotherapy-free regimen continues to be efficacious and safe for patients with CLL who either relapsed after or stopped responding to previous treatments.