Appendix 1. Schedules of Assessments

SCHEDULE OF ASSESSMENTS (TREATMENT ARM A: AV)

		Treatment Period (Each Cycle is 28 Days)							Post-Treatment Period		
									SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
		Cycle 1	Cycle 2	Cycle 3				Cycles 4–*14*	30 Days from Last Dose		
	Screening	Day 1	Day 1	Day 1	Day 8	Day 15	Day 22	Day 1		Q12W/Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3		±14/±28	±30
Study Drug Administration											
Acalabrutinib[d] (PO)		Continuous 100 mg BID dosing									
Venetoclax[e] (PO)				20 mg	50 mg	100 mg	200 mg	Continuous 400 mg QD through end of C*14*			
Procedures											
Informed consent	X										
Confirm eligibility and randomize	X										
Medical history	X										
Physical examination[f]	X	X	X	X				X	X	X	
Height	X										
Weight	X	X	X	X				X	X	X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	
RAI stage	*X*										
ECOG Performance status	X	X	X	X				X	X	X	
B-symptoms	X	X	X	X				X		X	
CIRS-G[h]	X										
ECG[i]	X										
Local serum hCG[j]	X	X							X		
Hematology[k]	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[l]	X	X	X	X	X	X	X	X	X	X	
TLS risk assessment				*X*							
Hepatitis serology[m]	X										

		Treatment Period (Each Cycle is 28 Days)							Post-Treatment Period		
									SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
		Cycle 1	Cycle 2	Cycle 3				Cycles 4–*14*	30 Days from Last Dose		
	Screening	Day 1	Day 1	Day 1	Day 8	Day 15	Day 22	Day 1		Q12W/Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3		±14/±28	±30
HBV PCR [n]	X		X	X				QM/Q12W, as appropriate		QM/Q12W, as appropriate	QM/Q12W, as appropriate
HCV PCR [o]	X										
CMV testing [p]	X										
Beta-2-microglobulin		X									
Serum immunoglobulins, T/B/NK/monocyte counts	X	X		X				C*6, C9, C12*		*12 weeks after end of treatment then* Q24W	
Central lab FISH and karyotyping (17p, TP53 testing, *and IGHV mutational status*)	X										
Medical resources utilization		X	X	X	X	X	X	X		X	
CT/MRI scan[q]	X			*X*				C9		12 weeks after end of treatment	
Response assessment[r]				*X*				C7, C9, C12	X	X	
BM biopsy and aspirate[s]	*X (optional)*							To confirm CR		12 weeks after end of treatment	
BM aspirate (flow-MRD)	X[t] (optional)							C9		12 weeks after end of treatment	
PB sample (flow-MRD)	X[t]			*X*				C*6*, C9, C12*, and end of C14*	X	Q12W *after end of treatment through 144 weeks then Q24*	
PB sample (NGS-MRD)[u]	X[t]							*C6,* C9, C12*, and end of C14*	X	Q12W/Q24W	
PB sample for ctDNA [v]	X[t]							C9 only			
PB sample for exploratory biomarker research[w]	X[t]								X		

		Treatment Period (Each Cycle is 28 Days)							Post-Treatment Period		
									SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
		Cycle 1	Cycle 2	Cycle 3				Cycles 4–*14*	30 Days from Last Dose		
	Screening	Day 1	Day 1	Day 1	Day 8	Day 15	Day 22	Day 1		Q12W/Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3		±14/±28	±30
Pharmacogenetic Research Sample (optional)[x]	X										
EORTC-QLQ-C30[y]		X	X	X				X	X	X	
FACIT-Fatigue[y]		X	X	X				X	X	X	
IL27[y]		X	X	X				X	X	X	
EQ-5D-5L[y]		X	X	X				X	X	X	
PGIS[y]		X	X	X				X	X	X	
PGIC[y]		X	X	X				X	X	X	
PK sample[z]		X						C5 and C7 only			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Adverse events[aa]	X	X	X	X	X	X	X	X	X	X	X
Collection of anti-CLL therapy										X	X
Survival status											X

AE=adverse event; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; BID=twice daily; BM=bone marrow; BTK=Bruton tyrosine kinase; C=cycle; CIRS-G=Cumulative Illness Rating Scale – Geriatric; CLL=chronic lymphocytic leukemia; CMV=cytomegalovirus; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L= EuroQoL five dimensions, five level; FACIT-Fatigue=fatigue-related quality of life as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue; FISH=fluorescence in situ hybridization; HBV=hepatitis B virus; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; IGHV=immunoglobulin heavy-chain variable; IL27=Item Library 27; IVIG= intravenous immunoglobulins; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not applicable; NGS=next generation sequencing; NK=natural killer; PB=peripheral blood; PCR=polymerase chain reaction; PGIC=Patient Global Assessment of Change; PGIS=Patient Global Assessment of Severity; PK=pharmacokinetic; PLCγ=phospholipase C gamma; PO=by mouth; PRO=patient-reported outcome; Q12W=every 12 weeks; Q24W=every 24 weeks; QD=once daily; QM=every month; SFU=safety follow-up; TLS=tumor lysis syndrome.

Footnotes for ACE-CL-311 Schedule of Study Activities for Treatment Arm A: Acalabrutinib and Venetoclax (AV):

a. An SFU visit is required 30 days after the last dose of the last study drug when subjects discontinue all study drugs, to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

b. Post-treatment follow-up: If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment follow-up visits should occur until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical examinations, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Post-treatment follow-up will be performed every 12 weeks for approximately 3 years (144 weeks), then every 24 weeks thereafter until disease progression, death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

c. Survival follow-up: Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every year by clinic visit or telephone, to assess survival and subsequent anti-CLL therapy until death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

d. Acalabrutinib to continue until *14* cycles of treatment are completed, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurs first.

e. Venetoclax schedule for ramp-up beginning at Cycle 3 Day 1 will be per label (see Table 1 for ramp-up schedule). Starting Cycle 4 Day 1, venetoclax dose will be 400 mg/day, continued through end of Cycle *14* for a total duration of *12* cycles or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurs first. Subjects may require hospitalization during the ramp-up period depending on their TLS risk. Refer to Section 4.3.2.2 (Table 4).

f. The physical examination includes examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, and lymphatic system and general appearance. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of *palpable* spleen and liver sizes below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic examinations for a given subject.

g. Vital signs (blood pressure, heart rate, and temperature*)* will be assessed after the subject has rested in the sitting position.

h. CIRS-G scoring is to be performed by a qualified provider.

i. Subjects should be in supine position and resting for ≥10 minutes before the baseline ECG.

j. Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. A serum pregnancy test is to be performed on Day 1 and at the SFU visit and may be performed more frequently if required by local regulatory authorities. If highly effective contraception is still required per protocol, then an additional pregnancy test should also be performed at the time point when highly effective contraception is no longer required per protocol.

k. Hematology: CBC with differential, including but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, neutrophil count, and lymphocyte count. Laboratory evaluations must be performed on the date specified, ±3 days. Hematology results must be confirmed by central laboratory and done within 7 days of CT/MRI scans.

l. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Creatinine clearance will also be assessed at Screening. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Local chemistry laboratory results may be used to monitor electrolytes for TLS during the venetoclax ramp-up and should be performed at the time points specified in Section 4.3.2.2 (Table 4).

m. Hepatitis serology must include HbsAg, anti-HBs, anti-HBc, and HCV antibody (see exclusion criteria #15).

n. Subjects who are anti-HBc positive must have quantitative PCR testing for HBV DNA performed during Screening and on study. These subjects should have a quantitative PCR test every 12 weeks during treatment and until 12 months after the last dose of study drug(s). In addition, anti-HBc positive subjects who received anti-CD20 therapy within the 12 months prior to study enrollment should have a quantitative PCR test monthly during treatment, regardless of current study treatment, for at least 12 months after last exposure to anti-CD20 therapy. After that, HBV PCR monitoring should continue every 12 weeks until at least 12 months after the last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, PCR testing every month is not required in subjects who are currently receiving or

received prophylactic IVIG within 12 weeks before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

o. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during Screening. No further testing beyond Screening is necessary if PCR results are negative.

p. CMV testing at Screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at Screening.

q. CT/MRI scans to be completed at the time points shown, with response evaluations (±14 days). CT scans and bone marrow biopsies may be performed within 14 days of the specified dates. Screening CT scans may be used if obtained as standard-of-care within *35* days prior to initiating treatment. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable.

r. Response evaluations will be done at the time points shown (±14 days). If response assessments coincide with additional assessment dates, only one set of applicable laboratory tests, CT scans, BM biopsies, etc. need to be completed for one overall response. Response evaluations should be completed during the Treatment Period and the Post-Treatment Period, until the subject has progressive disease.

s. A BM aspirate and biopsy sample *may* be collected at Screening (an archival sample may be used if collected ≤12 weeks before enrollment), *if performed*. BM aspirate/biopsy to be performed at the time points shown. BM biopsies/aspirates to confirm a CR must be done within 12 weeks of the CT/MRI scan that showed suspected CR. *A portion of BM biopsy from Screening or archival sample may be used for MRD assessments by NGS method. The disease follow-up sample may be taken 12 weeks after end of treatment.*

t If BM flow-MRD, PB flow-MRD, PB NGS-MRD, ctDNA, and exploratory biomarker research samples are not collected or damaged during collection/shipment at Screening, they will be collected at C1D1 (predose).

u. Samples for MRD by NGS will not be collected in Chinese subjects

v. This sample will not be collected in Chinese subjects.

w. *This sample will not be collected in Chinese subjects*.

x. This *saliva* sample will be collected at the baseline visit (screening or Cycle 1 Day 1) but may be collected at any time during the study or at a separate post-study visit, if necessary. *This sample will not be collected in Chinese subjects.*

y. The following PROs will be administered: EORTC-QLQ-C30), FACIT-Fatigue, additional items selected from *IL27*; PGIS of cancer symptoms; PGIC; and EQ-5D-5L health state utility index. PROs will be assessed prior to any other study procedures. *Must be taken prior to first dosing.*

z. PK samples to be collected before dosing (-30 minutes), 1 hour (±15 minutes) after dosing, and 4 hours (±30 minutes) after dosing, except for Cycle 1 Day 1 when only postdose samples will be collected. *On the day of sampling, the subject will not take a dose of any study drug before arrival at the clinic*.

aa. Before the first dose of any study drug, serious adverse events must be reported. After the end of the protocol-defined AE reporting period, only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

SCHEDULE OF ASSESSMENTS (TREATMENT ARM B: AVG)

		Treatment Period (Each Cycle is 28 Days)										Post-Treatment Period		
												SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
	Screening	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 2 Day 8	Cycle 2 Day15	Cycle 3 Day1	Cycle 3 Day 8	Cycle 3 Day 15	Cycle 3 Day 22	Cycles 4–*14* Day 1	30 Days from Last Dose	Q12W/ Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±14/±28	±30
Study Drug Administration														
Acalabrutinib[d] (PO)		Continuous 100 mg BID dosing												
Venetoclax[e] (PO)							20 mg	50 mg	100 mg	200 mg	Continuous 400 mg QD through end of C*14*			
Obinutuzumab[f] (IV)			100 mg	900 mg	1000 mg	1000 mg	1000 mg				1000 mg, C4 through C7			
Procedures														
Informed consent	X													
Confirm eligibility and randomize	X													
Medical history	X													
Physical examination[g]	X	X	X				X				X	X	X	
Height	X													
Weight	X	X	X				X				X	X	X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rai stage	*X*													
ECOG Performance status	X	X	X				X				X	X	X	

		Treatment Period (Each Cycle is 28 Days)										Post-Treatment Period		
												SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
	Screening	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 2 Day 8	Cycle 2 Day15	Cycle 3 Day1	Cycle 3 Day 8	Cycle 3 Day 15	Cycle 3 Day 22	Cycles 4–*14* Day 1	30 Days from Last Dose	Q12W/ Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±14/±28	±30
B-symptoms	X	X	X				X				X		X	
CIRS-G[j]	X													
ECG[j]	X													
Local serum hCG[k]	X	X										X		
Hematology[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	
TLS risk assessment							*X*							
Hepatitis serology[n]	X													
HBV PCR[o]	X		X				X				QM/Q12W, as appropriate		QM/Q12W, as appropriate	QM/Q12W, as appropriate
HCV PCR[p]	X													
CMV testing[q]	X													
Beta-2-microglobulin		X												
Serum immunoglobulins, T/B/NK/monocyte counts	X	X					X				*C6*, *C9, C12*		*12 weeks after end of treatment then* Q24W	
Central lab FISH and karyotyping (17p, TP53, *and IGHV mutational status* testing)	X													

		Treatment Period (Each Cycle is 28 Days)										Post-Treatment Period		
												SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
	Screening	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 2 Day 8	Cycle 2 Day15	Cycle 3 Day1	Cycle 3 Day 8	Cycle 3 Day 15	Cycle 3 Day 22	Cycles 4–*14* Day 1	30 Days from Last Dose	Q12W/ Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±14/±28	±30
Medical resources utilization		X	X	X	X	X	X	X	X	X	X		X	
CT/MRI scan[r]	X						*X*				C*9*		12 weeks after end of treatment	
*R*esponse assessment[s]							*X*				C7, C*9*, C12	X	X	
BM biopsy and aspirate[t]	*X (optional)*										To confirm CR		12 weeks after end of treatment	
BM aspirate (flow-MRD)	X[u] (optional)										C*10*		12 weeks after end of treatment	
PB sample (flow-MRD)	X[u]						*X*				C*6*, C*10*, C12, *and end of C14*	X	Q12W *after end of treatment through 144 weeks then Q24W*	
PB sample (NGS-MRD)[v]	X[u]										C*6, C10*, C12*, and* end of C14	X	Q12W/ Q24W	
PB sample for ctDNA[w]	X[u]										C*10* only			
PB sample for exploratory biomarker research[x]	X[u]											X		

		Treatment Period (Each Cycle is 28 Days)										Post-Treatment Period		
												SFU Visit[a]	Post-Treatment *Disease* Follow-Up[b]	Post-Progression Survival Follow-Up[c]
	Screening	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 2 Day 8	Cycle 2 Day15	Cycle 3 Day1	Cycle 3 Day 8	Cycle 3 Day 15	Cycle 3 Day 22	Cycles *4–14* Day 1	30 Days from Last Dose	Q12W/ Q24W	Yearly
Study Windows (days)	*35*		±3	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±14/±28	±30
Pharmacogenetic Research Sample (optional)[y]	X													
EORTC-QLQ-C30[z]		X	X				X				X	X	X	
FACIT-Fatigue[z]		X	X				X				X	X	X	
IL27[z]		X	X				X				X	X	X	
EQ-5D-5L[z]		X	X				X				X	X	X	
PGIS[z]		X	X				X				X	X	X	
PGIC[z]		X	X				X				X	X	X	
PK sample[aa]		X									C5 and C7 only			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[bb]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collection of anti-CLL therapy													X	X
Survival status														X

AE=adverse event; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; BID=twice daily; BM=bone marrow; BTK=Bruton tyrosine kinase; C=cycle; CIRS-G=Cumulative Illness Rating Scale – Geriatric; CLL=chronic lymphocytic leukemia; CMV=cytomegalovirus; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L= EuroQoL five dimensions, five level; FACIT-Fatigue=fatigue-related quality of life as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue; FISH=fluorescence in situ hybridization; HBV=hepatitis B virus; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; IGHV=immunoglobulin heavy-chain variable; IVIG= intravenous immunoglobulins; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not applicable; NGS=next generation sequencing; NK=natural killer; PB=peripheral blood; PCR=polymerase chain reaction; PGIC=Patient Global Assessment of Change; PGIS=Patient Global Assessment of Severity; PK=pharmacokinetic; PLCγ=phospholipase C gamma; PO=by mouth; PRO=patient-reported outcome; Q12W=every 12 weeks; Q24W=every 24 weeks; QD=once daily; QM=every month; SFU=safety follow-up; TLS=tumor lysis syndrome.

Footnotes for ACE-CL-311 Schedule of Study Activities for Treatment Arm B: Acalabrutinib, Venetoclax, and Obinutuzumab (AVG):

a A SFU visit is required 30 days after the last dose of the last study drug when subjects discontinue all study drugs, to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

b Post-treatment follow-up: If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment follow-up visits should occur until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical examinations, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Post-treatment follow-up will be performed every 12 weeks for approximately 3 years (144 weeks), then every 24 weeks thereafter until disease progression, death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

c Survival follow-up: Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every year by clinic visit or telephone, to assess survival and subsequent anti-CLL therapy until death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

d Acalabrutinib to continue until *14* cycles of treatment are completed, or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurs first.

e Venetoclax schedule for ramp-up beginning at Cycle 3 Day 1 will be per label (see Table 2 for ramp-up schedule). Starting Cycle 4 Day 1, venetoclax dose will be 400 mg/day, continued through end of Cycle *14* for a total duration of *12* cycles or until start of new anti-CLL therapy or progression of CLL, or unacceptable toxicity, whichever occurs first. Subjects may require hospitalization during the ramp-up period depending on their TLS risk. Refer to Section 4.3.2.2 (Table 4).

f Obinutuzumab will be given intravenously starting on Cycle 2 Day 1 and will continue for a total of 6 cycles. During the first cycle that obinutuzumab is given, drug will be administered on Day 1 at 100 mg, Day 2 at 900 mg, then Day 8 and 15 at 1000 mg. For subsequent cycles (Cycles 3-7), obinutuzumab will be given on Day 1 at 1000 mg.

g The physical examination includes examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, and lymphatic system and general appearance. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of *palpable* spleen and liver sizes below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

h Vital signs (blood pressure, heart rate, and temperature) will be assessed after the subject has rested in the sitting position.

i CIRS-G scoring is to be performed by a qualified provider.

j Subjects should be in supine position and resting for ≥10 minutes before the baseline ECG.

k Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. A serum pregnancy test is to be performed on Day 1 and at the SFU visit and may be performed more frequently if required by local regulatory authorities. If highly effective contraception is still required per protocol, then an additional pregnancy test should also be performed at the time point when highly effective contraception is no longer required per protocol.

l Hematology: CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, neutrophil count, and lymphocyte count. Laboratory evaluations must be performed on the date specified, ±3 days. Hematology results must be confirmed by central laboratory and done within 7 days of CT/MRI scans.

m Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Creatinine clearance will also be assessed at Screening. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Local chemistry lab may be used to monitor electrolytes for TLS during the venetoclax ramp-up and should be performed at the time points specified in Section 4.3.2.2 (Table 4).

n Hepatitis serology must include HbsAg, anti-HBs, anti-HBc, and HCV antibody (see exclusion criteria #15).

o Subjects who are anti-HBc positive must have quantitative PCR testing for HBV DNA performed during Screening and on study. Anti-HBc positive subjects who receive combination therapy with obinutuzumab should have a quantitative PCR test monthly during treatment and until 12 months after the last dose of obinutuzumab. In addition, anti-HBc positive subjects who received anti-CD20 therapy within the 12 months prior to study enrollment should also have a quantitative PCR test monthly during treatment, regardless of current study treatment, for at least 12 months after last exposure to anti-CD20 therapy. After that, HBV PCR monitoring should continue every 12 weeks until at least 12 months after the last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, PCR testing every month is not required in subjects who are currently receiving or received prophylactic IVIG within 12 weeks before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

p Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during Screening. No further testing beyond Screening is necessary if PCR results are negative.

q CMV testing at Screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at Screening.

r CT/MRI scans to be completed at the time points shown, with response evaluations (±14 days). CT scans and bone marrow biopsies may be performed within 14 days of the specified dates. Screening CT scans may be used if obtained as standard-of-care within *35* days prior to initiating treatment. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable.

s Response evaluations will be done at the time points shown (±14 days). If response assessments coincide with additional assessment dates, only one set of applicable laboratory tests, CT scans, BM biopsies, etc. need to be completed for one overall response. Response evaluations should be completed during the Treatment Period and the Post-Treatment Period, until the subject has progressive disease.

t A BM aspirate and biopsy sample *may* be collected at Screening (an archival sample may be used if collected ≤12 weeks before enrollment), *if performed*. BM aspirate/biopsy to be performed at the time points shown. BM biopsies/aspirates to confirm a CR must be done within 12weeks of the CT/MRI scan which showed suspected CR. *A portion of BM aspirate, or biopsy from Screening or archival sample maybe used for MRD assessments by NGS method. The disease follow-up sample may be taken 12 weeks after end of treatment.*

u If BM flow-MRD, PB flow-MRD, PB NGS-MRD, ctDNA, and exploratory biomarker research samples are not collected or damaged during collection/shipment at Screening, they will be collected at C1D1 (predose).

v Samples for MRD by NGS will not be collected in Chinese subjects.

w This sample will not be collected in Chinese subjects.

x *This sample will not be collected in Chinese subjects.*

y This *saliva* sample will be collected at the baseline visit (screening or Cycle 1 Day 1) but may be collected at any time during the study or at a separate post-study visit, if necessary. *This sample will not be collected in Chinese subjects.*

z The following PROs will be administered: EORTC-QLQ-C30, FACIT-Fatigue; additional items selected from *IL27*; PGIS of cancer symptoms; PGIC; and EQ-5D-5L health state utility index. PROs will be assessed prior to any other study procedures. *Must be taken prior to first dosing.*

aa PK samples to be collected before dosing (-30 minutes), 1 hour (±15 minutes) after dosing, and 4 hours (±30 minutes) after dosing, except for Cycle 1 Day 1 when only postdose samples will be collected.

bb Before the first dose of any study drug, serious adverse events must be reported. After the end of the protocol-defined AE reporting period, only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

SCHEDULE OF ASSESSMENTS (TREATMENT ARM C: BR)

		Treatment Period (Each Cycle is 28 Days)						Post-Treatment Period		
								SFU[a]	Post-Treatment *Disease* Follow-Up[b]	Post-*Progression* Survival Follow-Up[c]
		Cycle 1				Cycles 2–6		30 Days from Last Dose		
	Screening	Day 1	Day 2	Day 8	Day 15	Day 1	Day 2		Q12W/Q24W	Yearly
Study Windows (days)	*35*	±3				±3		N/A	±14/±28	±30
Study Drug Administration										
Bendamustine[d] (IV)		90 mg/m^2	90 mg/m^2			90 mg/m^2	90 mg/m^2			
Rituximab[e] (IV)		375 mg/m^2				500 mg/m^2				
Procedures										
Informed consent	X									
Confirm eligibility & randomize	X									
Medical history	X									
Physical examination[f]	X	X				X		X	X	
Height	X									
Weight	X	X				X		X	X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	
Rai stage	*X*									
ECOG Performance Status	X	X				X		X	X	
B-symptoms	X	X				X			X	
CIRS-G[h]	X									
ECG[i]	X									
Local serum hCG[j]	X	X						X		
Hematology[k]	X	X	X	X	X	X		X	X	
Serum chemistry[l]	X	X	X	X	X	X		X	X	
Hepatitis serology[m]	X									
HBV PCR[n]	X					QM/Q12W, as appropriate			Q12W, as appropriate	Q12W, as appropriate
HCV PCR[o]	X									
CMV testing[p]	X									
β2-microglobulin		X								
Serum immunoglobulins, T/B/NK/monocyte counts	X	X				*C3 and C6*			Q24W *from C6D1*	

		Treatment Period (Each Cycle is 28 Days)						Post-Treatment Period		
								SFU[a]	Post-Treatment *Disease* Follow-Up[b]	Post-*Progression* Survival Follow-Up[c]
		Cycle 1				Cycles 2–6		30 Days from Last Dose		
	Screening	Day 1	Day 2	Day 8	Day 15	Day 1	Day 2		Q12W/Q24W	Yearly
Study Windows (days)	*35*	±3				±3		N/A	±14/±28	±30
Central lab FISH and karyotyping (17p, TP53*, and IGHV mutational status* testing)	X									
Medical resources utilization		X	X	X	X	X	X		X	
CT/MRI scans[q]	X					C*3*			12 weeks after C6D1 only	
*R*esponse assessments[r]						C*3*		X	X	
BM biopsy and aspirate[s]	*X (optional)*					To confirm CR			12 weeks after C6D1 only	
BM aspirate (flow-MRD)	X[t] (optional)								12 weeks after C6D1	
PB sample (flow-MRD)	X[t]					C*3* and C6		X	Q12W *from C6D1 through Week 144 and then* Q24W *after*	
PB sample (NGS-MRD)[u]	*X*[t]					C6			*Q12W/Q24W after C6*	
PB sample for ctDNA[v]	X[t]								*12* weeks after C6D1	
PB sample for exploratory biomarker research [w]	X[t]							X		
Pharmacogenetic Research Sample (optional)[x]	X									
EORTC-QLQ-C30[y]		X				X		X	X	
FACIT-Fatigue [y]		X				X		X	X	
IL27 [y]		X				X		X	X	
EQ-5D-5L [y]		X				X		X	X	
PGIS [y]		X				X		X	X	
PGIC [y]		*X*				X		X	X	

		Treatment Period (Each Cycle is 28 Days)						Post-Treatment Period		
								SFU[a]	Post-Treatment *Disease* Follow-Up[b]	Post-*Progression* Survival Follow-Up[c]
		Cycle 1				Cycles 2–6		30 Days from Last Dose		
	Screening	Day 1	Day 2	Day 8	Day 15	Day 1	Day 2		Q12W/Q24W	Yearly
Study Windows (days)	*35*	±3				±3		N/A	±14/±28	±30
Concomitant medications	X	X	X	X	X	X	X	X		
Adverse events[z]	X	X	X	X	X	X	X	X	X	X
Collection of anti-CLL therapy									X	X
Survival status										X

AE=adverse event; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; AST=aspartate aminotransferase; BID=twice daily; BM=bone marrow; BTK=Bruton tyrosine kinase; BUN=blood urea nitrogen; C=cycle; CBC=complete blood count; CIRS-G=Cumulative Illness Rating Scale – Geriatric; CLL=chronic lymphocytic leukemia; CMV=cytomegalovirus; CR=complete response; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; HBV=hepatitis B virus; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; IGHV=immunoglobulin heavy-chain variable; IVIG= intravenous immunoglobulins; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not applicable; NGS=next generation sequencing; NK=natural killer; PB=peripheral blood; PCR=polymerase chain reaction; PK=pharmacokinetic; PLCγ=phospholipase C gamma; PO=by mouth; PRO=patient-reported outcome; Q12W=every 12 weeks; Q24W=every 24 weeks; QD=once daily; QM=every month; SFU=safety follow-up.

Footnotes for ACE-CL-311 Schedule of Study Activities for Treatment Arm C: Bendamustine/Rituximab:

a An SFU visit is required 30 days after the last dose of the last study drug when subjects discontinue all study drugs, to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

b Post-treatment follow-up: If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment follow-up visits should occur until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical examinations, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Post-treatment follow-up will be performed every 12 weeks for approximately 3 years (144 weeks), then every 24 weeks thereafter until disease progression, death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

c Survival follow-up: Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every year by clinic visit or telephone, to assess survival and subsequent anti-CLL therapy until death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

d Bendamustine 90 mg/m^2 will be administered as an IV infusion on Days 1 and 2 of a 28-day cycle according to the instructions and precautions in locally approved labelling and institutional standards. Accommodations should be made in the event of doses of bendamustine held or delayed due to toxicity to permit a full 6 cycles to be received, wherever possible. A maximum of 6 cycles can be administered.

e Rituximab will be administered intravenously at a dosage of 375 mg/m2 in the first cycle and at a dose of 500 mg/m2 in Cycles 2–6 according to the instructions and precautions in the locally approved labelling and per institutional standards.

f The physical examination includes examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, and lymphatic system and general appearance. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of *palpable* spleen and liver sizes below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

g Vital signs (blood pressure, heart rate, and temperature) will be assessed after the subject has rested in the sitting position.

h CIRS-G scoring is to be performed by a qualified provider.

i Subjects should be in supine position and resting for ≥10 minutes before the baseline ECG.

j Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. A serum pregnancy test is to be performed on Day 1 and at the SFU visit and may be performed more frequently if required by local regulatory authorities. If highly effective contraception is still required per protocol, then an additional pregnancy test should also be performed at the time point when highly effective contraception is no longer required per protocol.

k Hematology: CBC with differential, including but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, neutrophil count, and lymphocyte count. Laboratory evaluations must be performed on the date specified, ±3 days. Hematology results must be confirmed by central laboratory and done within 7 days of CT/MRI scans.

l Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Creatinine clearance will also be assessed at Screening. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

m Hepatitis serology must include HbsAg, anti-HBs, anti-HBc, and HCV antibody (see exclusion criteria #15).

n Subjects who are anti-HBc positive must have quantitative PCR testing for HBV DNA performed during Screening and on study. These subjects should have a quantitative PCR test every 12 weeks during treatment and until 12 months after the last dose of study drug(s). In addition, anti-HBc positive subjects who received anti-CD20 therapy within the 12 months prior to study enrollment should have a quantitative PCR test monthly during treatment, regardless of current study treatment, for at least 12 months after last exposure to anti-CD20 therapy. After that, HBV PCR monitoring should continue every 12 weeks until at least 12 months after the last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, PCR testing every month is not required in subjects who are currently receiving or received prophylactic IVIG within 12 weeks before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

o Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during Screening. No further testing beyond Screening is necessary if PCR results are negative.

p CMV testing at Screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at Screening.

q CT/MRI scans to be completed at the time points shown, with response evaluations (±14 days). CT scans and bone marrow biopsies may be performed within 14 days of the specified dates. Screening CT scans may be used if obtained as standard-of-care within *35* days prior to initiating treatment. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable.

r Response evaluations will be done at the time points shown (±14 days). If response assessments coincide with additional assessment dates, only one set of applicable laboratory tests, CT scans, BM biopsies, etc. need to be completed for one overall response. Response evaluations should be completed during the Treatment Period and the Post-Treatment Period, until the subject has progressive disease.

s A BM aspirate and biopsy sample will be collected at Screening (an archival sample may be used if collected ≤12 weeks before enrollment). BM aspirate/biopsy to be performed at the time points shown. BM biopsies/aspirates to confirm a CR must be done within 12 weeks of the CT/MRI scan which showed suspected CR. If BM biopsy/aspirate was performed to confirm CR within the prior 90 days, then no additional biopsy/aspirate is necessary. *A portion of BM aspirate, or biopsy from screening or archival sample maybe used for MRD assessments by NGS method. The disease follow-up sample may be taken 12 weeks after end of treatment.*

t *If BM flow-MRD, PB flow-MRD, PB NGS-MRD, ctDNA, and exploratory biomarker research samples are not collected or damaged during collection/shipment at Screening, they will be collected at C1D1 (predose).*

u Samples for MRD by NGS will not be collected in Chinese subjects

v This sample will not be collected in Chinese subjects.

w *This will be collected at C1D1. This sample will not be collected in Chinese subjects.*

x This *saliva* sample will be collected at the baseline visit (screening or Cycle 1 Day 1) but may be collected at any time during the study or at a separate post-study visit, if necessary. *This sample will not be collected in Chinese subjects.*

y The following PROs will be administered: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30); fatigue-related quality of life as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue); additional items selected from *IL27*; patient global impression of severity of cancer symptoms (PGIS); patient global impression of change (PGIC); and EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index. PROs will be assessed prior to any other study procedures. *Must be taken prior to first dosing.*

z Before the first dose of any study drug, serious adverse events must be reported. After the end of the protocol-defined AE reporting period, only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

SCHEDULE OF ASSESSMENTS (TREATMENT ARM C: FCR)

		Treatment Period (Each Cycle is 28 Days)						Post-Treatment Period		
		Cycle 1			Cycles 2–6			SFU[a]	Post-Treatment Follow-Up[b]	Post-Progression Survival Follow-up[c]
	Screening	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	30 Days from Last Dose	Q12W/Q24W	*Yearly*
Study Windows (days)	*35*	±3			±3			N/A	±14/±28	±30
Study Drug Administration										
Fludarabine[d] (IV)		25 mg/m^2	25 mg/m^2	25 mg/m^2	25 mg/m^2	25 mg/m^2	25 mg/m^2			
Cyclophosphamide[e] (IV)		250 mg/m^2	250 mg/m^2	250 mg/m^2	250 mg/m^2	250 mg/m^2	250 mg/m^2			
Rituximab[f] (IV)		375 mg/m^2			500 mg/m^2					
Procedures										
Informed consent	X									
Confirm eligibility & randomize	X									
Medical history	X									
Physical examination[g]	X	X			X			X	X	
Height	X									
Weight	X	X			X			X	X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	
Rai stage	*X*									
ECOG Performance Status	X	X			X			X	X	
B-symptoms	X	X			X				X	
CIRS-G[i]	X									
ECG[j]	X									
Local serum hCG[k]	X	X						X		
Hematology[l]	X	X	X	X	X			X	X	
Serum Chemistry[m]	X	X	X	X	X			X	X	
Hepatitis serology[n]	X									
HBV PCR[o]					QM/Q12W as appropriate				QM/Q12W as appropriate	QM/Q12W as appropriate

		Treatment Period (Each Cycle is 28 Days)						Post-Treatment Period		
		Cycle 1			Cycles 2–6			SFU[a]	Post-Treatment Follow-Up[b]	Post-Progression Survival Follow-up[c]
	Screening	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	30 Days from Last Dose	Q12W/Q24W	*Yearly*
Study Windows (days)	*35*	±3			±3			N/A	±14/±28	±30
HCV PCR[p]	X									
CMV testing[q]	X									
β2-microglobulin		X								
Serum immunoglobulins, T/B/NK/monocyte counts	X				C3 *and C6*				Q24W *from C6D1*	
Central lab FISH and karyotyping (17p, TP53 testing, *and IGHV mutational status*)	X									
Medical resources utilization	X	X	X	X	X	X	X		X	
CT/MRI scans[r]	X				C*3* only				12 weeks after C6D1 only	
*R*esponse assessment[s]					C*3* only			X	X	
BM biopsy and aspirate[t]	*X (optional)*				To confirm CR				12 weeks after C6D1 only	
BM aspirate (flow-MRD)[u]	X[v] (optional)								12 weeks after C6D1 only	
PB sample (flow-MRD)[w]	X[v]				C*3* and C6 only			X	Q12W *from C6D1 through Week 144 and then* Q24W *after through end of study*	
PB sample (NGS-MRD)[w]	*X[v]*				C6				*Q12W/Q24W after C6D1*	

		Treatment Period (Each Cycle is 28 Days)						Post-Treatment Period		
								SFU[a]	Post-Treatment Follow-Up[b]	Post-Progression Survival Follow-up[c]
		Cycle 1			Cycles 2–6			30 Days from Last Dose		
	Screening	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3		Q12W/Q24W	*Yearly*
Study Windows (days)	*35*	±3			±3			N/A	±14/±28	±30
PB sample for ctDNA[w]	X[v]								*12* weeks after C6D1	
PB sample for exploratory biomarker research[x]	X[v]							X		
Pharmacogenetic Research Sample (optional)[y]	X									
EORTC-QLQ-C30[z]		X			X			X	X	
FACIT-Fatigue[z]		X			X			X	X	
IL27[aa]		X			X			X	X	
EQ-5D-5L[aa]		X			X			X	X	
PGIS[aa]		X			X			X	X	
PGIC[aa]		*X*			X			X	X	
Concomitant medications	X	X	X	X	X	X	X	X		
Adverse events[bb]	X	X	X	X	X	X	X	X	X	X
Collection of anti-CLL therapy									X	X
Survival status										X

AE=adverse event; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; AST=aspartate aminotransferase; BID=twice daily; BM=bone marrow; BTK=Bruton tyrosine kinase; BUN=blood urea nitrogen; C=cycle; CBC=complete blood count; CIRS-G=Cumulative Illness Rating Scale – Geriatric; CLL=chronic lymphocytic leukemia; CMV=cytomegalovirus; CR=complete response; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; HBV=hepatitis B virus; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; IGHV=immunoglobulin heavy-chain variable; IVIG= intravenous immunoglobulins; MRD=minimal residual disease; MRI=magnetic resonance imaging; N/A=not applicable; NGS=next generation sequencing; NK=natural killer; PB=peripheral blood; PCR=polymerase chain reaction; PK=pharmacokinetic; PLCy=phospholipase C gamma; PO=by mouth; PRO=patient-reported outcome; Q12W=every 12 weeks; Q24W=every 24 weeks; QD=once daily; QM=every month; SFU=safety follow-up.

Footnotes for ACE-CL-311 Schedule of Study Activities for Treatment Arm C: Fludarabine, Cyclophosphamide and Rituximab:

a A SFU visit is required 30 days after the last dose of the last study drug when subjects discontinue all study drugs, to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe.

b Post-treatment follow-up: If disease progression has not occurred at the time of the 30-day SFU visit, post-treatment follow-up visits should occur until disease progression, regardless of whether the subject receives a new anticancer therapy. During this period, subjects will be followed for disease progression via CT/MRI scans, CBC with differential, physical examinations, serum chemistry, and bone marrow biopsy and aspirate (as clinically indicated). Post-treatment follow-up will be performed every 12 weeks for approximately 3 years (144 weeks), then every 24 weeks thereafter until disease progression, death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

c Survival follow-up: Once subjects progress—for all subjects who have not withdrawn consent—they will be contacted approximately every year by clinic visit or telephone, to assess survival and subsequent anti-CLL therapy until death, withdrawal of consent by subject, loss to follow-up, or study terminated by sponsor, whichever occurs first.

d Fludarabine 25 mg/m^2 will be administered as an IV infusion on Days 1–3 of a 28-day cycle for a maximum of 6 cycles according to the instructions and precautions in the locally approved labelling and per institutional standards.

e Cyclophosphamide 250 mg/m^2 will be administered as an IV infusion on Days 1–3 of a 28-day cycle for a maximum of 6 cycles according to the instructions and precautions in the locally approved labelling and per institutional standards.

f Rituximab will be administered intravenously at a dosage of 375 mg/m^2 in the first cycle and at a dose of 500 mg/m^2 in Cycles 2–6 according to the instructions and precautions in the locally approved labelling and per institutional standards.

g The physical examination includes examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, and lymphatic system and general appearance. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of *palpable* spleen and liver sizes below the costal margin on the respective side. Only physicians, physician assistants, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given subject.

h Vital signs (blood pressure, heart rate, and temperature) will be assessed after the subject has rested in the sitting position.

i CIRS-G scoring is to be performed by a qualified provider.

j Subjects should be in supine position and resting for ≥10 minutes before the baseline ECG.

k Serum pregnancy testing, per the Schedule of Assessments, will be required only for women of childbearing potential. A serum pregnancy test is to be performed on Day 1 and at the SFU visit and may be performed more frequently if required by local regulatory authorities. If highly effective contraception is still required per protocol, then an additional pregnancy test should also be performed at the time point when highly effective contraception is no longer required per protocol.

l Hematology: CBC with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, neutrophil count, and lymphocyte count. Laboratory evaluations must be performed on the date specified, ±3 days. Hematology results must be confirmed by central laboratory and done within 7 days of CT/MRI scans.

m Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Creatinine clearance will also be assessed at Screening. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

n Hepatitis serology must include HbsAg, anti-HBs, anti-HBc, and HCV antibody (see exclusion criteria #15).

o Subjects who are anti-HBc positive must have quantitative PCR testing for HBV DNA performed during Screening and on study. These subjects should have a quantitative PCR test every 12 weeks during treatment and until 12 months after the last dose of study drug(s). In addition, anti-HBc positive subjects who received anti-CD20 therapy within the 12 months prior to study enrollment should have a quantitative PCR test monthly during treatment, regardless of current study treatment, for at least 12 months after last exposure to anti-CD20 therapy. After that, HBV PCR monitoring should continue every 12 weeks until at least 12 months after the last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, PCR testing every month is not required in subjects who are currently receiving or received prophylactic IVIG within 12 weeks before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

p Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during Screening. No further testing beyond Screening is necessary if PCR results are negative.

q CMV testing at Screening must include serologic testing for CMV immunoglobulin G (CMV IgG), CMV IgM, and CMV DNA PCR testing. Subjects must have a result for CMV DNA PCR which is below the lower limit of quantitation at Screening.

r CT/MRI scans to be completed at the time points shown, with response evaluations (±14 days). CT scans and bone marrow biopsies may be performed within 14 days of the specified dates. Screening CT scans may be used if obtained as standard-of-care within *35* days prior to initiating treatment. Radiologic imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck (and any other disease area). Subjects who are intolerant to intravenous CT contrast agents will have CT scans performed with oral contrast. MRI may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable.

s Response evaluations will be done at the time points shown (±14 days). If response assessments coincide with additional assessment dates, only one set of applicable laboratory tests, CT scans, BM biopsies, etc. need to be completed for one overall response. Response evaluations should be completed during the Treatment Period and the Post-Treatment Period, until the subject has progressive disease.

t A BM aspirate and biopsy sample will be collected at Screening (an archival sample may be used if collected ≤12 weeks before enrollment). BM aspirate/biopsy to be performed at the time points shown. BM biopsies/aspirates to confirm a CR must be done within 8–12 weeks of the CT/MRI scan which showed suspected CR. If BM biopsy/aspirate was performed to confirm CR within the prior 90 days, then no additional biopsy/aspirate is necessary. *A portion of BM aspirate, or biopsy from screening or archival sample maybe used for MRD assessments by NGS method. The disease follow-up sample may be taken 12 weeks after end of treatment.*

u This sample will not be collected in Chinese subjects.

v If BM flow-MRD, PB flow-MRD, PB NGS-MRD, ctDNA, and exploratory biomarker research samples are not collected or damaged during collection/shipment at Screening, they will be collected at C1D1 (predose).

w *If collection is missed on Screening, this will be collected at C1D1. This sample will not be collected in Chinese subjects.*

x This *saliva* sample will be collected at the baseline visit (screening or Cycle 1 Day 1) but may be collected at any time during the study or at a separate post-study visit, if necessary. *This sample will not be collected in Chinese subjects.*

y The following PROs will be administered: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30); fatigue-related quality of life as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue); additional items selected from *IL27*; patient global impression of severity of cancer symptoms (PGIS); patient global impression of change (PGIC); and EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index. PROs will be assessed prior to any other study procedures. *Must be taken prior to first dosing.*

z Before the first dose of any study drug, serious adverse events must be reported. After the end of the protocol-defined AE reporting period, only serious adverse events considered related to study drug(s) or study procedures are required to be collected.

aa *Diagnostic archival samples (formalin-fixed paraffin-embedded, etc.) will be used for NGS-based MRD evaluation. If BM biopsy/aspirate for CR confirmation was performed within 90 days of Cycle 9 and Cycle 12, and 12 weeks after end of Cycle 14, collect additional samples for NGS-based MRD evaluation. Samples for MRD by NGS will not be collected in Chinese subjects.*