IV. Baseline assessments at screening (for all patients)

- ☐ Informed consent
- ☐ Inclusion-/Exclusion Criteria
- ☐ CIRS Score /Medical history
- ☐ ECOG /Disease-related B-symptoms
- ☐ Concomitant Medication
- ☐ Height / Weight / BSA
- ☐ Physical examination
- ☐ Blood withdrawal for:
    - **Complete blood count**
      (including differential count: white blood cell count (WBC), hemoglobin, platelet count, absolute neutrophil and absolute lymphocyte count (ANC, ALC) and reticulocytes)
    - **Serum chemistry**
      (serum creatinine, total bilirubin, AST, ALT, LDH, sodium, potassium, calcium, phosphorus, chloride, uric acid, blood urea nitrogen (BUN), immunoglobulins (IgA, IgM, IgG, IgE) and direct antiglobulin Coombs test)
    - **HIV / HBV / HCV test**
      (≤6 weeks prior to randomization. Patients who are HBsAg negative/anti-HBc positive may be included if PCR for HBV DNA (with a lower limit of detection of the order of 10 WHO IU/mL) is negative and HBV-DNA PCR is performed every month until 1 year after last dosage of antibody. If the HBV DNA assay becomes positive, patients should preemptively be treated with a nucleoside analog (i.e. tenofovir or entecavir) for at least twelve months after the last cycle of therapy or be referred to a gastroenterologist for management
    - **Beta-2-MG** (to be sent to central lab Cologne)
    - **Immunophenotyping + genome sequencing + karyotyping** (to be sent to central lab Cologne)
    - **FISH cytogenetics, TP53 and IGHV** (to be sent to central lab Ulm)
    - **Accompanying scientific program** (to be sent to central lab Ulm)
- ☐ Pregnancy test (for all women of childbearing potential)
- ☐ Radiological assessment of lymphadenopathy, liver and spleen using imaging techniques (CT or MRI) ECG and, if clinically indicated, echocardiogram for evaluation of left ventricular ejection fraction (LVEF)
- ☐ Bone marrow aspirate/biopsy in case CLL infiltration of the bone marrow must be proven (see inclusion criterion 5)
- ☐ Health-related quality of life by EORTC QLQ-C30 and QLQ-CLL16

V. Study assessment table (SCIT)

		HBV testing[2]	Pregnancy test[3]	Concomittant Medication	ECOG / disease-related B-symptoms	Height / Weight / BSA	Physical examination	Radiological assessment[4]	ECG / LVEF	Complete blood count[5]	Serum chemistry[6]	Quality of life (QoL)[7]	FISH cytogenetics, TP53 and IGHV (central lab Ulm)	MRD from peripheral blood (central lab Kiel)	Accompanying scientific program	Bone marrow aspirate/biopsy[8]	MRD from bone marrow[8] (central lab Kiel)	Response assessment	New treatment and survival status	i.v. administration of Rituximab	i.v. administration of Bendamustin	i.v. administration of Fludarabine and Cyclophosphamid	(serious) adverse events[9]
Cycle 1-6	**day 1[1]**	(x)	(x)	CONTINUOUS REPORTING		X	O			X	X			X[10]	X[11, 12]					X	X	X	CONTINUOUS REPORTING
	days 2/(3)																				X	X	
	days 8/15/22									O	O												
Interim staging[13]					X		X	(x)	O	X	X	X	X[12]		X[12]			X	X				
Initial response assessment[14]					X		X	(x)	O	X	X	X	X[12]		X[12]			X	X				
Final restaging[15]		(x)	(x)		X		X	X	O	X	X		X[12]		X[12]	X	X	X	X				
MRD-Staging 1[16]									O			X	X[12]	X	X[12]			X	X				
MRD-Staging 2 [MO13][17]		(x)			X		X	(x)	O	X	X	X	X[12]	X	X[12]			X	X				
MRD-Staging 3 [MO15][18]		(x)			X		X	(x)	O	X	X	X	X[12]	X	X[12]			X	X				
Follow-up until PD[19]		(x)			X		X	(x)	O	X	O	X[20]	X[12]		X[12]			X	X				
Follow-up after PD[21]					X				O			X[20]						X	X				

X = assessment mandatory, (x) = assessment mandatory in certain patients/situations, O = assessment recommended, but not documented in the CRF.

For all tests in the study a time window of +/- 2 days is appropriate.

1) Treatment must be started within 14 days after randomization
2) Only for patients who are HBsAg negative/anti-HBc positive with negative PCR for HBV DNA (with a lower limit of detection of the order of 10 WHO IU/mL) at screening; in this case HBV-DNA PCR must be performed every month until 1 year after last dosage of rituximab. If the HBV DNA assay becomes positive, patients should pre-emptively be treated with a nucleoside analog (i.e. tenofovir or entecavir) for at least twelve months after the last cycle of therapy or be referred to a gastroenterologist for management.
3) ≤7 days before start of study treatment and on day 1 of every treatment cycle (monthly) in all women of childbearing potential
4) Radiological assessment of lymphadenopathy, liver and spleen using imaging techniques (CT or MRI) must be performed at final restaging (if abnormal at screening). The modality of staging in one patient should not be changed. Further imaging (even with ultrasound) can be performed at the investigator's discretion, e.g. in case of a suspected PD.
5) including differential count: white blood cell count (WBC), hemoglobin, platelet count, absolute neutrophil and absolute lymphocyte count (ANC, ALC) and reticulocytes
6) serum creatinine, total bilirubin, AST, ALT, LDH, sodium, potassium, calcium, phosphorus, chloride, uric acid and blood urea nitrogen (BUN) [required at all time points]; immunoglobulins (IgA, IgM, IgG, IgE) and direct antiglobulin Coombs test [at final restaging]
7) EORTC QLQ-C30 and EORTC QOL-CLL16 questionnaires only (MARS not required)
8) Bone marrow aspirate/biopsy must be performed locally at final restaging. In parallel an additional bone marrow aspirate sample for MRD measurement has to be sent to the central lab in Kiel preferably together with MRD-testing of peripheral blood at MRD-staging 1 (Final Restaging)
9) For reporting timelines and further details please refer to section *11.1 Reporting periods*.
10) Samples for MRD testing should be sent to central lab in Kiel on cycle 1 day 1 and cycle 2 day 1
11) Samples for accompanying scientific program should be sent to Kiel and Ulm on cycle 2 day 1
12) To be sent in case of progression
13) = Staging after 3 cycles of treatment, to be performed before administration of rituximab and chemotherapy on day 1 of cycle 4
14) = Staging after last cycle of treatment, should take place 28 days after start of last treatment cycle administered
15) should take place three month after start of last treatment cycle administered (two month after initial response assessment), preferably together with MRD-Staging 1 [approximately 9 month after start of treatment = MO9]
16) MRD assessment three month after start of last treatment cycle administered, preferably performed together with the staging procedures of final restaging [approximately 9 month after start of treatment = MO9]
17) approximately 13 month after start of treatment) [= MO12] at the assumed timepoint of cycle 12 day 28, preferably together with a follow-up visits (+/- 30 day window
18) 2 month after MRD-Staging 2 [approximately 15 month after start of treatment = MO15]
19) starting at final restaging, mandatory every 3 month until progression or end of study, whatever occurs first (for quality of life see point 20)
20) EORTC QLQ-C30 and EORTC QOL-CLL16 questionnaires should be answered annually starting at 24 month after initiation of treatment
21) Follow-up after PD will be performed annually until the end of study

VI. Study assessment table (RVe/GVe/GIVe) and venetoclax ramp-up-schedule

		HBV testing[2]	Pregnancy test[3]	Concomittant Medication	ECOG / disease-related B-symptoms	Height / Weight / BSA	Physical examination	Radiological assessment[4]	ECG / LEVF	Complete blood count[5]	Serum chemistry[6]	Quality of life (QoL)[7]	FISH cytogenetics, TP53 and IGHV (central lab Ulm)	MRD from peripheral blood (central lab Kiel)	Accompanying scientific program	Bone marrow aspirate/biopsy[8]	MRD from bone marrow (central lab Kiel)[8]	Response assessment	New treatment and survival status	i.v. administration of Rituximab[9]	i.v. administration of Obinutuzumab[10]	Drug accountability and dispense Venetoclax	p.o. administration of Venetoclax	Drug accountability and dispense Ibrutinib	p.o. administration of Ibrutinib	(serious) adverse events[11]
Cycle 1-6	day 1[1]	(x)	(x)	CONTINUOUS REPORTING		X	O			X[12]	X[12]		X[13]	X[14]	X[15,13]					X	X[16]	X	DAILY[17]	X	DAILY[18]	CONTINUOUS REPORTING
	days 8/15/22									O	O															
Interim staging I / II / III[19]					X		X	(x)	O	X	X	X	X[13]		X[13]			X	X							
Cycle 7-12 (day 1)		(x)	(x)				O			X	X		X[13]		X[13]							X	DAILY[17]	X		
MRD-Staging 1[20]		(x)			X		X	(x)	O	X	X	X	X[13]	X	X[13]			X	X							
MRD-Staging 2[21]		(x)			X		X	(x)	O	X	X	X	X[13]	X	X[13]			X	X			X		X		
Final restaging[22]		(x)			X		X	X	O	X	X		X[13]		X[13]	X	X	X	X							
MRD-Staging 3 [MO15][23]		(x)			X		X	(x)	O	X	X	X[24]	X[13]		X[13]	X	X	X	X					(x)		
Follow-up until PD[25]		(x)			X		X	(x)	O	X	O	X[24,26]	X[13]	X	X[13]			X	X					(x)		
Follow-up after PD[27]		(x)			X							X[26]		X[28]				X	X					(x)		

X = assessment mandatory, (x) = assessment mandatory in certain patients/certain situations,
O = assessment recommended and to the investigator´s discretion, but <u>not</u> documented in the CRF (except for lab testing during venetoclax ramp-up as described in the venetoclax ramp-up schedule).

For all tests in the study a time window of +/- 2 days is appropriate.

Reassessment of TLS risk for dosing at home is possible until cycle 1 day 20.

1) Treatment must be started within 14 days after randomization

2) Only for patients who are HBsAg negative/anti-HBc positive with negative PCR for HBV DNA (with a lower limit of detection of the order of 10 WHO IU/mL) at screening; in this case HBV-DNA PCR must be performed every month until 1 year after last dosage of rituximab or obinutuzumab respectively. If the HBV DNA assay becomes positive, patients should pre-emptively be treated with a nucleoside analog (i.e. lamivudine) for at least twelve months after the last cycle of therapy or be referred to a gastroenterologist for management.

3) ≤7 days before start of study treatment and on day 1 of every treatment cycle (monthly) in all women of childbearing potential

4) Radiological assessment of lymphadenopathy, liver and spleen using imaging techniques (CT or MRI) is mandatory at final restaging (if abnormal at screening). The modality of staging in one patient should not be changed. Further imaging (even with ultrasound) can be performed at the investigator's discretion, e.g. in case of a suspected PD or for TLS risk reassessment before cycle 1 day 20.

5) including differential count: white blood cell count (WBC), hemoglobin, platelet count, absolute neutrophil and absolute lymphocyte count (ANC, ALC) and reticulocytes

6) serum creatinine, total bilirubin, AST, ALT, LDH, sodium, potassium, calcium, phosphate, chloride, uric acid and blood urea nitrogen (BUN) [required at all timepoints]; immunoglobulins (IgA, IgM, IgG, IgE) and direct antiglobulin Coombs test [at final restaging]

7) EORTC QLQ-C30, EORTC QOL-CLL16 and MARS questionnaires (MARS questionnaire only as long as Venetoclax or Ibrutinib are taken)

8) Bone marrow aspirate/biopsy must be performed locally at final restaging. In parallel an additional bone marrow aspirate sample for MRD measurement has to be sent to the central lab in Kiel preferably together with MRD-testing of peripheral blood at MRD-staging 3 (Final Restaging)

9) For patients randomized to the RVe arm

10) For patients randomized to the GVe or GIVe arm

11) For reporting timelines and further details please refer to section *11.1 Reporting periods*.

12) During first dose and dose escalations of venetoclax several lab assessments are necessary, see *8.4.4 Laboratory monitoring*. Also, administrative details (hospitalization, length of stay, administration of allopurinol and rasburicase) will be captured.

13) To be sent in case of progression

14) Samples for MRD testing should be sent to central lab in Kiel on cycle 1 day 1 and cycle 2 day 1

15) Additional samples for accompanying scientific program should be sent to Kiel and Ulm on cycle 2 day 1

16) Split first dose of obinutuzumab (100mg/900mg) at cycle 1 day 1/2; additional doses at days 8 and 15 of the first cycle

17) Venetoclax will be started on cycle 1 day 22 with a weekly dose ramp-up (20mg – 50mg – 100mg – 200mg – 400mg) until the maximum dose of 400mg is reached. During first dose and dose escalations of venetoclax several lab assessments are necessary, see Venetoclax ramp-up schedule.

18) For patients in the GIVe arm only; Ibrutinib will be started on cycle 1 day 1 (in the morning before breakfast) with a daily oral intake of 420mg until MRD-negativity is reached in patients with CR or a maximum of 36 month or new CLL treatment or progression, whatever occurs first.

19) = Staging after 3 (cycle 4 day 1), 6 (cycle 7 day 1) and 9 cycles of treatment (cycle 10 day 1, preferably together with MRD-staging 1); to be performed before administration of the antibody (if applicable)

20) Staging performed on cycle 10 day 1 [approximately 9 month after start of treatment = MO9] (Please note: If treatment was stopped prematurely this staging can be skipped

21) = Initial response assessment; Staging after last cycle of treatment, should take place 28 days after start of last treatment cycle administered (preferably one day after the last intake of venetoclax) [approximately 13 month after start of treatment = MO12]

22) Three month after start of last treatment cycle administered (ideally cycle 12); if treatment was stopped prematurely and final restaging **can not** be performed together with MRD-staging 3 an **additional MRD-sample** (PB) should be taken

23) At the assumed timepoint of regularly planned final restaging (ideally 2 month after end of 12 treatment cycles, +/- 30 days window), even if treatment was stopped prematurely

24) EORTC QLQ-C30 and EORTC QOL-CLL16; MARS only for patients in the GIVe arm of the trial (as long as ibrutinib is taken)

25) starting at final restaging, mandatory every 3 month until progression or end of study, whatever occurs first (for quality of life see point 26)

26) EORTC QLQ-C30 and EORTC QOL-CLL16 should be answered annually starting at 24 month after initiation of treatment

27) Follow-up after PD will be performed annually until the end of study

28) MRD measurements at later timepoints might be evaluated according to the discretion of the treating physician at local laboratories

Venetoclax ramp-up schedule

	Cycle1		Cycle 2							
Day	***22***	***23***	***1***	***2***	***8***	***9***	***15***	***16***	***22***	***23***
Venetoclax dose	20 mg		50 mg		100 mg		200 mg		400 mg	
TLS Lab-Based Risk Assessment and monitoring[1]	X	X	X	X	X	X	X	X	X	X
Hospitalisation	(X)[2]		(X)[2]		(X)[2]		(X)[2]		(X)[2]	

X = assessment mandatory, (x) = assessment mandatory in certain patients/certain situations[2]

[1]) Chemistry and hematology must be assessed predose* as well as 6 - 8 and 24 hours after the first venetoclax dose and predose* as well as 6 - 8 and 24 hours after each new (increased) venetoclax dose during the venetoclax dose-ramp up phase.

[2]) Hospitalisation is recommended for patients at increased risk for TLS (ALC > 50.000 x 109/L) on the first days of 20 mg and 50 mg doses and possibly day 1 of 100 mg, 200 mg and 400 mg doses. For further details please see worksheet „TLS risk management".

*predose: Labs should be drawn before venetoclax administration and results must be reviewed prior to dosing.

In patients where **dosing at home** is performed, assessment must take place within **24 hours** (including review of the results) prior to dosing. An additional lab must be performed **within 2 hours after intake** (as soon as the patients arrives at hospital/outpatient department).

In all other cases (including patients with increased risk or hospitalized patients) pre-dose labs should be drawn up to **up to 4 hours before venetoclax administration**, and results must be reviewed prior to dosing.
If it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take an **additional** predose chemistry sample within **24 hours** prior to dosing. The results of the sample taken within 24 hours prior to dosing must be reviewed prior venetoclax application.