SUPPLEMENTARY APPENDIX

Bendamustine followed by ofatumumab and ibrutinib in chronic lymphocytic leukemia: primary endpoint analysis of a multicenter, open-label, phase II trial (CLL2-BIO)

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Supplementary appendix for manuscript HAEMATOL/2019/223693:

Bendamustine, followed by ofatumumab and ibrutinib in chronic lymphocytic leukemia: primary endpoint analysis of the CLL2-BIO phase-II trial

METHODS:

Table S1: Recruiting sites:

Site	Principal Investigator	Number of pts screened
University Hospital Cologne	Dr. Paula Cramer	18
University Hospital Würzburg	PD. Dr. Werner J. Heinz	8
Tagesklinik Landshut	Dr. Ursula Vehling-Kaiser	7
University Hospital Essen	Prof. Dr. Jan Dürig	6
University Hospital Ulm	Prof. Dr. Stephan Stilgenbauer	6
Mannheimer Onkologie Praxis	Prof. Dr. Manfred Hensel	5
Gemeinschaftspraxis Dres. Mohm/Prange-Krex, Dresden	Dr. Johannes Mohm	4
Praxis Dres. Jacobs/Daus/Schmits, Saarbrücken	Dr. Georg Jacobs	3
PIOH Frechen	Dr. Holger Schulz	3
University Hospital Heidelberg	Prof. Dr. Peter Dreger	2
Hospital Schwabing, Munich	Dr. Clemens Wendtner	2
Caritas Klinikum, Saarbrücken	Prof. Dr. Michael Clemens	2
University Hospital Schleswig Holstein, Kiel	PD. Dr. Sebastian Böttcher	1
MVZ für Blut- und Krebserkrankungen, Potsdam	Dr. Hartmut Linde	1

Eligibility criteria

In addition to standard eligibility criteria (see below), patients were required to have an adequate haematological function with a platelet count ≥25,000 per µL, a neutrophil count ≥1,000 per µL, and a haemoglobin value ≥8 g/dL (unless directly attributable to the patient´s CLL), as well as a creatinine clearance of at least 30 mL/min and an adequate liver function. Excluded were patients with a Richter´s transformation, secondary malignancy or uncontrolled infection requiring systemic treatment, patients with a history of stroke or intracranial haemorrhage within 6 months prior to registration and patients taking strong CYP3A4 inhibitors/inducers or vitamin k-antagonists.

Inclusion Criteria:

1. Documented CLL requiring treatment (irrespective if first- or relapse treatment) according to iwCLL criteria
   In case of previously treated patients, these must have recovered from acute toxicities and treatment regimen must be stopped within the following time periods before start of the study treatment in the CLL2-BIO trial:
   - chemotherapy within ≥ 28 days
   - antibody treatment within ≥ 14 days

- kinase inhibitors, BCL2-antagonists or immunmodulatory agents within ≥ 3 days
- corticosteroids may be applied until the start of the BIO-regimen, these have to be reduced to an equivalent of ≤ 20mg prednisolone during treatment

2. Adequate hematologic function as indicated by a platelet count ≥ 25 x 10^9/L, a neutrophil count ≥ 1,0 x 10^9/L and a hemoglobin value ≥8.0 g/dL, unless directly attributable to the patient´s CLL (e.g. bone marrow infiltration)
3. Adequate renal function, as indicated by a creatinine clearance ≥30ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured with 24 hr. urine collection
4. Adequate liver function as indicated by a total bilirubin ≤ 2x, AST/ALT ≤ 2.5x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome
5. Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative, patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every two months until 6 months after last dosage of ofatumumab), negative testing for hepatitis-C RNA and negative HIV test within 6 weeks prior to registration
6. Age ≥ 18 years
7. ECOG 0 to 2, ECOG 3 is only permitted if related to CLL (e.g. due to anemia or severe constitutional symptoms)
8. Life expectancy ≥ 6 months
9. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements

Exclusion criteria:

1. Transformation of CLL (i.e. Richter's transformation, prolymphocytic leukemia)
2. Known central nervous system (CNS) involvement
3. Patients with confirmed PML
4. Malignancies other than CLL currently requiring systemic therapy
5. Uncontrolled infection requiring systemic treatment
6. Any comorbidity or organ system impairment rated with a CIRS (cumulative illness rating scale) score of 4, excluding the eyes/ears/nose/throat/larynx organ system* or any other life-threatening illness, medical condition or organ system dysfunction that – in the investigator´s opinion - could compromise the patients safety or interfere with the absorption or metabolism of the study drugs (e.g, inability to swallow tablets or impaired resorption in the gastrointestinal tract)
7. Use of investigational agents which might interfere with the study drug within 3 days prior to registration
8. Known hypersensitivity to ofatumumab, ibrutinib or any of the excipients
   Please note: Patients with a known hypersensitivity to bendamustine are allowed to participate but will not receive a debulking with bendamustine
9. Requirement of treatment with strong CYP3A4-inhibitors/inducers or anticoagulant with phenprocoumon (marcumar), warfarin, or other vitamin-k antagonists
10. History of stroke or intracranial hemorrhage within 6 months prior to registration
11. Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment and monthly during debulking, induction and maintenance therapy)
12. Fertile men or women of childbearing potential unless:
    - surgically sterile or ≥ 2 years after the onset of menopause, or
    - willing to use two methods of reliable contraception including one highly effective (Pearl Index <1) and one additional effective (barrier) method during study treatment and for 12 months after end of study treatment.
13. Vaccination with a live vaccine ≤28 days prior to registration

*) The CIRS score rates of the burden of comorbidity in each organ system with 0 to 4 points. This rating may be performed according to the guidelines by Salvi et. al. (Journal of the American geriatrics Society, 2008), which provide a point value for several different comorbidities. However, these guidelines are not binding and the treating physician´s assessment of the severity should outweigh the point value according to the Salvi guidelines. For example, a pulmonary embolism is related with 4 points according to Salvi guidelines, which means "Life threatening illness/impairment, emergency case of therapy, adverse prognosis" and would preclude trial participation, in case the pulmonary embolism occurred some time ago the treating physician may rate this history of pulmonary embolism with a lower point value and include the patient into the trial.

14. Legal incapacity
15. Prisoners or subjects who are institutionalized by regulatory or court order
16. Persons who are in dependence to the sponsor or an investigator

Assessments

At baseline, diagnosis of chronic lymphocytic leukaemia was confirmed centrally by immunophenotyping of circulating lymphocytes and all relevant prognostic parameters (including cytogenetic aberrations by means of fluorescence in-situ hybridization, mutational analysis of the immunoglobulin heavy-chain variable-region gene (IGHV) and tumour protein 53 (*TP53*), as well as the serum parameters beta$_2$-microglobulin and thymidine kinase) were assessed in the central laboratories of the German CLL Study Group in Cologne and Ulm. A central screening process prevented inclusion of patients with an incorrect diagnosis or other violations of eligibility criteria.

Minimal residual disease (MRD) samples mostly from peripheral blood and also bone marrow were taken from the final restaging after the induction treatment onwards at three- to six-monthly intervals (based on the IWCLL response achieved). The samples were analysed centrally in the reference laboratory in Kiel with four-color flow cytometry.(14, 15) Results were categorised into three different MRD levels: low ($<10^{-4}$), intermediate ($\geq10^{-4}$ and $<10^{-2}$) and high ($\geq10^{-2}$)(16) and MRD negativity was defined as $<10^{-4}$.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0 and classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system.

Outcomes

The primary endpoint of the CLL2-BIO trial was the overall response rate (ORR) by investigator assessment after induction treatment, assessed at the final restaging 12 weeks after the start of the last induction cycle and defined as the proportion of patients having achieved a complete remission(CR/CRi) or partial response (PR).

Secondary endpoints included the ORR after debulking and maintenance treatment, the ORR in predefined subgroups (according to previous treatment, physical fitness, cytogenetic abnormalities, IGHV mutational status, TP53 mutation, and administration of debulking treatment), complete remission (CR) rates, best response rate achieved until six months after final restaging, MRD assessments in peripheral blood and bone marrow, as well as safety analyses and time to event analyses for progression-free survival (defined as the time between registration and first disease progression or death) and overall survival (defined as the time between registration and death). Other secondary endpoints will be analysed later with extended follow-up data.

Statistical analyses

The primary endpoint (ORR by investigator assessment after induction treatment) was used to calculate the sample size of the study. The ORR was tested against the null hypothesis of 75% using a two-sided binomial test. The BIO-regimen was expected to lead to an improvement of the ORR from 75% (with bendamustine/rituximab)(17, 18) to 90%. 54 patients were required to have 80% power at a two-sided significance level of 5%. In consideration of an expected drop-out rate of 10%, we aimed to recruit 62 analysable patients. Concerning different allocations of untreated and relapsed/refractory patients a fix lower limit of at least 21 patients (1/3 of planned patient number) in each cohort needed to be enrolled.

Results presented in this publication are based on the pre-defined efficacy population, which includes all patients who received at least two complete cycles of induction treatment. All patients included into the trial and treated with at least one dose of study treatment were considered in the safety analyses. Results of primary and secondary endpoints were described for the mixed population and for the two cohorts of treatment-naïve and relapsed/refractory patients separately.

The 95% exact confidence interval (CI) for the ORR was calculated according to the Clopper-Pearson method. Sensitivity analyses were not done for the primary endpoint analysis. The Kaplan-Meier method was used for time-to-event analyses. Rate based endpoints and other characteristics were summarized by counts and percentages.

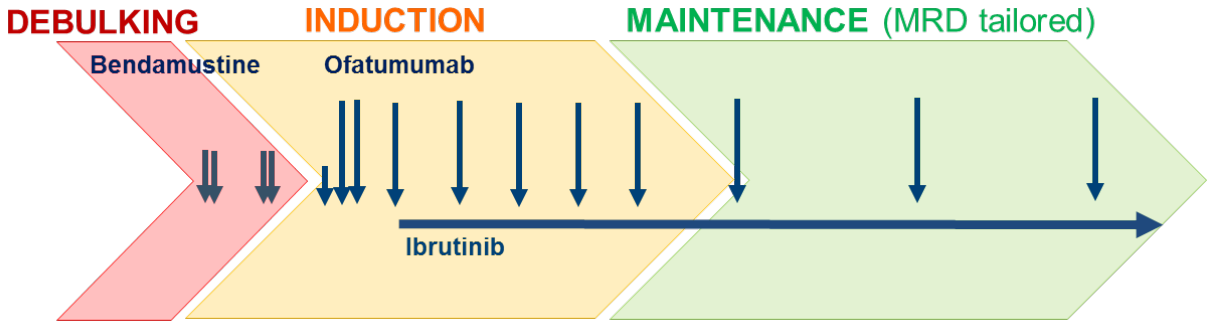
The primary endpoint analysis was performed on a dataset with data cut-off date 4th April 2018, with a median observation time of 20 months (range: 15 to 31 months; interquartile range (IQR): 18 to 22 months). Analyses were done using SPSS (version 24) and SAS (version 9.4).

Role of the funding source:

The pharmaceutical companies Novartis and Glaxo-Smith-Kline provided financial support, the study drugs ofatumumab and ibrutinib were provided by Novartis and Janssen-Cilag, respectively. The pharmaceutical companies did neither influence trial design, data collection, analysis and interpretation, nor the content of this manuscript.

The first author wrote the manuscript draft, all authors reviewed and approved the final version, no professional medical-writing services were used.

Figure S1: BIO study treatment



DEBULKING (2 cycles with a duration of 28 days): **Bendamustine**

should be omitted in case of:
contraindications for the usage of bendamustine (known hypersensitivity to bendamustine, refractoriness to bendamustine or chemotherapy-induced bone marrow damage) **or if not necessary due to low tumour burden** (ALC ≤25.000/µl and absence of bulky disease with lymph nodes ≤5 cm in the longest diameter)

Bendamustine:	cycles 1-2:	days 1 & 2:	70 mg/m² i.v.

INDUCTION (6 cycles with a duration of 28 days): **Ofatumumab & Ibrutinib**

Ofatumumab:	cycle 1:	day 1:	300 mg i.v.
		days 8 & 15:	1000 mg i.v.
	cycles 2-6:	day 1:	1000 mg i.v.
Ibrutinib:	cycles 2-6:	days 1-28:	420 mg (3 tablets) p.o.

MAINTENANCE (2-8 cycles with a duration of 84 days): **Ofatumumab & Ibrutinib**

will be continued until (whichever occurs first):
3 months after **achievement of (clinical) CR/CRi and MRD negativity** (confirmed by 2 measurements), completion of **24 months of maintenance** (8 cycles each with a duration of 84 calendar days), progression of CLL, start of new CLL treatment, or unacceptable toxicity.

Ofatumumab:	cycles 1-8:	day 1:	1000 mg i.v.
Ibrutinib:	cycles 1-8:	days 1-84:	420 mg (3 tablets) p.o.

Please note:

The additional ofatumumab infusion on day 15 of the first cycle was included to achieve higher plasma levels and facilitate a comparison with the similar CLL2-BIG phase-II trial evaluating a bendamustine debulking followed by ibrutinib combined with obinutuzumab instead of ofatumumab.

RESULTS:

Figure S2: Previous therapies (n=50) of the 26 relapsed/refractory patients

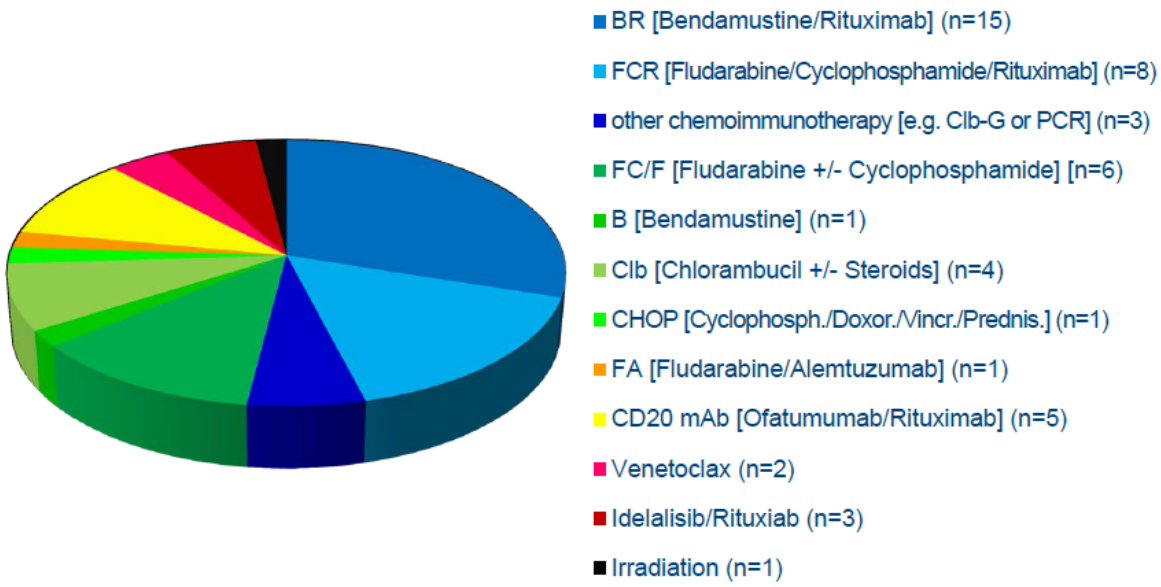


Table S2: Overall and MRD negative response at end of induction (Efficacy population)

	Overall response rate	MRD neg. rate (pB)*
All patients	**92%** (60 of 65 pts)	**14%** (9 of 65 pts)
by previous treatment		
- first-line	**100%** (39 of 39 pts)	**18%** (7 of 39 pts)
- relapsed/refractory	**81%** (21 of 26 pts)	**8%** (2 of 26 pts)
by fitness status		
- fit	**93%** (37 of 40 pts)	**13%** (5 of 40 pts)
- unfit	**92%** (23 of 25 pts)	**16%** (4 of 25 pts)
by cytogenetics**		
- del(17p)	**75%** (9 of 12 pts)	**0%** (0 of 12 pts)
- del(11q)	**100%** (12 of 12 pts)	**8%** (1 of 12 pts)
- trisomy 12	**100%** (10 of 10 pts)	**50%** (5 of 10 pts)
- none	**94%** (17 of 18 pts)	**11%** (2 of 18 pts)
- del(13q)	**92%** (12 of 13 pts)	**8%** (1 of 13 pts)
by *TP53* deficiency		
- del(17p) and/or *TP53* mut.	**81%** (17 of 21 pts)	**0%** (0 of 21 pts)
- none	**98%** (43 of 44 pts)	**20%** (9 of 44 pts)
by IGHV mutational status		
- IGHV mutated	**100%** (20 of 20 pts)	**25%** (5 of 20 pts)
- IGHV unmutated	**89%** (40 of 45 pts)	**9%** (4 of 45 pts)
by administration of debulking		
- debulking	**98%** (50 of 51 pts)	**14%** (7 of 51 pts)
- no debulking	**71%** (10 of 14 pts)	**14%** (2 of 14 pts)

*) 3 patients were lacking MRD assessment at final restaging at the end of induction treatment, these are considered MRD pos.
**) according to hierarchical model by Döhner et al.

Table S3: Fatalities

Septic shock with multiple organ failure after 6th induction cycle (related, unrelated according to investigator)	• 73 years old female patient • initial diagnosis of CLL in 12/2007, 5 prior therapies (3x chlorambucil/steroids and 2x bendamustine/rituximab), IGHV mutated and *TP53* mutated • CIRS score 4 (incl. asthma bronchiale and hypercholesterinaemia) • started treatment in 06/2016 without debulking and achieved a PR after induction • died of a septic shock with multiple organ failure after the 6th induction cycle.
Ischaemic cerebral infarction in 2nd mainentenance cycle (related)	• 73 years old male patient • initial diagnosis of CLL in February 2011, no prior therapy for CLL; IGHV unmut., del(17p) and *TP53* mut. • CIRS score 2 (pAVK) • pt started treatment in May 2016 with debulking and achieved a clinical CRi after induction • pt was hospitalized in the 2nd maintenance cycle due to a pneumonia, he developed a tachyarrythmia absoluta and sepsis; due to a fall and haemoptysis heparine treatment was discontinued. Later a cerebellar infarction was diagnosed and together with the patient´s family it was decided to refrain from a craniektomy and stop intensive care treatment for sepsis; the patient died of an ischaemic cerebral infarction with supra- and infratentorial herniation.

Table S4: Overview of all adverse events (Safety population):

Results are total numbers of adverse events and percentages (in brackets)

	treatment-naïve (n=40)	relapsed/refractory (n=26)	all patients (n=66)
ALL ADVERSE EVENTS (AEs)	602	357	959
AEs RELATED TO STUDY DRUG	391 (65%)	209 (59%)	600 (63%)
SERIOUS ADVERSE EVENTS (SAEs)	47 (8%)	40 (11%)	87 (9%)
CTC GRADE			
- CTC °I (mild/asymptomatic)	308 (51%)	160 (45%)	468 (49%)
- CTC °II (moderate)	225 (37%)	130 (36%)	355 (37%)
- CTC °III (severe/medically significant)	60 (10%)	60 (17%)	120 (13%)
- CTC °IV (life-threatening)	8 (1%)	6 (2%)	14 (2%)
- CTC °V (fatal)	1 (0.2%)	1 (0.3%)	2 (0.2%)
OUTCOME			
- resolved	462 (77%)	280 (78%)	742 (77%)
- resolved with sequelae	1 (0.2%)	1 (0.3%)	2 (0.2%)
- persisting	138 (23%)	75 (21%)	213 (22%)
- death	1 (0.2%)	1 (0.3%)	2 (0.2%)
ADUSTMENT OF STUDY DRUG:			
- none	516 (86%)	280 (78%)	796 (83%)
- dose reduction	21 (4%)	15 (4%)	36 (4%)
- interruption	66 (11%)	53 (15%)	119 (12%)
- permanent discontinuation	9 (2%)	16 (5%)	25 (3%)
- missing information	1 (0.2%)	1 (0.3%)	2 (0.2%)
TIME POINT OF OCCURRENCE:			
- debulking (2 months)	114 (19%)	44 (12%)	158 (16%)
- induction (8 months)	337 (56%)	210 (59%)	547 (57%)
- maintenance/follow-up (ongoing)	151 (25%)	103 (29%)	254 (26%)

Table S5: Adverse events considered most relevant and dosemodifications occurring in the induction phase in patients with versus without debulking (Safety population)
Results are total numbers of patients and percentages (in brackets)

	pts with debulking		pts without debulking	
Toxicity	(n=52)		(n=14)	
	any grade	CTC°III-V	any grade	CTC°III-V
Any adverse event	**52 (100%)**	**22 (42%)**	**14 (100%)**	**12 (86%)**
Blood and lymphatic system disorders:	**12 (23%)**	**9 (17%)**	**8 (57%)**	**7 (50%)**
- Neutropenias	8 (15%)	8 (15%)	6 (43%)	6 (43%)
- Thrombocytopenia	2 (4%)	-	2 (14%)	2 (14%)
Infections:	**33 (64%)**	**4 (8%)**	**9 (64%)**	**3 (21%)**
- Upper respiratory tract infections	16 (31%)	-	4 (29%)	-
- Lower respiratory tract and lung inf.	6 (12%)	2 (4%)	1 (7%)	-
- Infections NEC	5 (10%)	-	1 (7%)	1 (7%)
- Dental and oral soft tissue infections	3 (6%)	-	2 (14%)	-
- Urinary tract infections	3 (6%)	-	2 (14%)	-
- Abdominal and gastrointestinal infections	3 (6%)	1 (2%)	1 (7%)	1 (7%)
- Conjunctivitis	2 (4%)	-	2 (14%)	-
- Oral herpes	3 (6%)	-	1 (7%)	-
Injury/procedural complications:	**25 (48%)**	**3 (6%)**	**10 (71%)**	**3 (21%)**
- Infusion related reaction	20 (38%)	2 (4%)	9 (64%)	3 (21%)
- Spinal fractures and dislocations	2 (4%)	1 (2%)	1 (7%)	-
Metabolism and nutrition disorders:	**7 (14%)**	**-**	**2 (14%)**	**-**
Dose modifications	**(n=51)**		**(n=14)**	
Ibrutinib:				
- mean (range) dose intensity [% of planned dose]	95.4 (41 - 116)%		87.2 (31 - 101)%	
- any dose reduction	31 (61%)		9 (64%)	
- any treatment interruption	29 (57%)		8 (57%)	
- interruptions with a duration ≥7 days	14 (27%)		5 (36%)	
Ofatumumab:				
- mean (range) dose intensity [% of planned dose]	99.1 (73 - 106)		99.1 (88 - 100)	

DISCUSSION:

Table S6: Comparison of the BIO regimen with other CLL therapies

	Thrombocyto-penia	Neutropenia	Infections	ORR	CR/CRi rate	MRD neg. rate
BIO regimen in firstline cohort	**0%**	**18%**	**5%**	**100%**	**0%***	**18%** in PB
(Benadmustine)/Venetoclax/Obinutu-zumab (BAG) [Cramer et al., Lancet Oncol 2018]	3%	34%	9%	100%	9%	91% in PB 12% in BM
(Benadmustine)/Ibrutinib/Obinutuzu-mab (BIG) [v. Tresckow et al., Leukemia 2018]	10%	7%	NR	100%	0%	53% in PB
Ibrutinib/Obinutuzumab [Moreno et al., Lancet Oncol 2019]	°III: 15% °IV 4%	°III: 18% °IV 19%	NR	88%	19%	30% in PB 20% in BM[1]
Ibrutinib/Rituximab [Woyach et al., NEJM 2018]	NR	NR	NR	94%	12%	4% in BM
Ibrutinib [Woyach et al., NEJM 2018]	NR	NR	NR	93%	7%	1% in BM
Chlorambucil/Obinutuzumab [Goede et al., NEJM 2014; Moreno et al., Lancet Oncol 2019]	5-10%	33%	12%	73-78%	8-21%	20-38% in PB 17-20% in BM
Bendamustin/Rituximab [Fischer et al., J Clin Oncol 2012; Eichhorst et al., Lancet Oncol 2016, Woyach et al., NEJM 2018]	20-22%	20-59%	8-24%	81-96%	23-31%	22-38% in PB 6-11% in BM[2]
Fludarabin/Cyclophosphamide/ Rituximab [Keating et al., J Clin Oncol 2005; Hallek et al., Lancet 2010; Eichhorst et al., Lancet Oncol 2016]	7-21%	34-85%	25-38%	90-95%	40-70%	49% in PB 27% in BM[3]
BIO regimen in rel./refr. cohort	**8%**	**27%**	**19%**	**81%**	**0%***	**8%** in PB
(Benadmustine)/Venetoclax/Obinutuz umab (BAG) [Cramer et al., Lancet Oncol 2018]	23%	55%	29%	90%	7%	83% in PB 14% in BM
(Benadmustine)/Ibrutinib/Obinutuzum ab (BIG) [v. Tresckow et al., Leukemia 2018]	16%	23%	NR	100%	0%	42% in PB
Ibrutinib/Ofatumumab [Jaglowski et al, Blood 2015]	≤15%	24%	NR	83%	3%	NR
Ibrutinib/Rituximab [Burger et al, Lancet Oncol 2014, Burger et al., Blood 2018]	0%	5%	8%	89-95%	8-23%	5% in BM
Ibrutinib [Byrd et al, NEJM 2014; Byrd et al, Blood 2015, Burger et al., Blood 2018]	6-10%	15-18%	51%	63-92%	0-20%	1% in BM
Idelalisib/Rituximab [Furman et al, NEJM 2014]	10%	34%	NR	81%	0%	NR
Venetoclax [Roberts et al., NEJM 2016; Stilgenbauer et al., Lancet Oncol, 2016]	12-15%	40-41%	20%	79%	8-20%	17% in PB 5-6% in BM[4]
Venetoclax/Rituximab [Seymour et al., Lancet Oncol 2017; Seymour et al., NEJM 2018]	6-16%	53-58%	16-18%	86-92%	8-51%	84% in PB[5] 27-57% in BM[6]

BM = bone marrow; **CR/CRi** = rate of complete remissions, including those with incomplete recovery of the bone marrow; **MRD neg**. = minimal residual disease negativity rate; **NR** = not reported; **ORR** = overall response rate; **PB** = peripheral blood.

*) CR/CRi rate is expected to rise with ongoing maintenance treatment as several patients fulfill the IWCLL criteria but are lacking a confirmatory CT scan or bone marrow aspirate.

[1]) 38% (PB) and 25% (BM) of tested patients;
[2]) 58-63% (PB) and 30-32% (BM) of tested patients;
[3]) 74% (PB) and 58% (BM) of tested patients;
[4]) 40% (PB) and 35-60% (BM) of tested patients
[5]) 87% (PB in Murano trial) of tested pts
[6]) 67-76% (BM) of tested patients.