SUPPLEMENTARY APPENDIX

Outcome of advanced chronic lymphocytic leukemia following different first-line and relapse therapies: a meta-analysis of five prospective trials by the German CLL Study Group (GCLLSG)

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ACCOMPANYING MATERIAL for the manuscript:

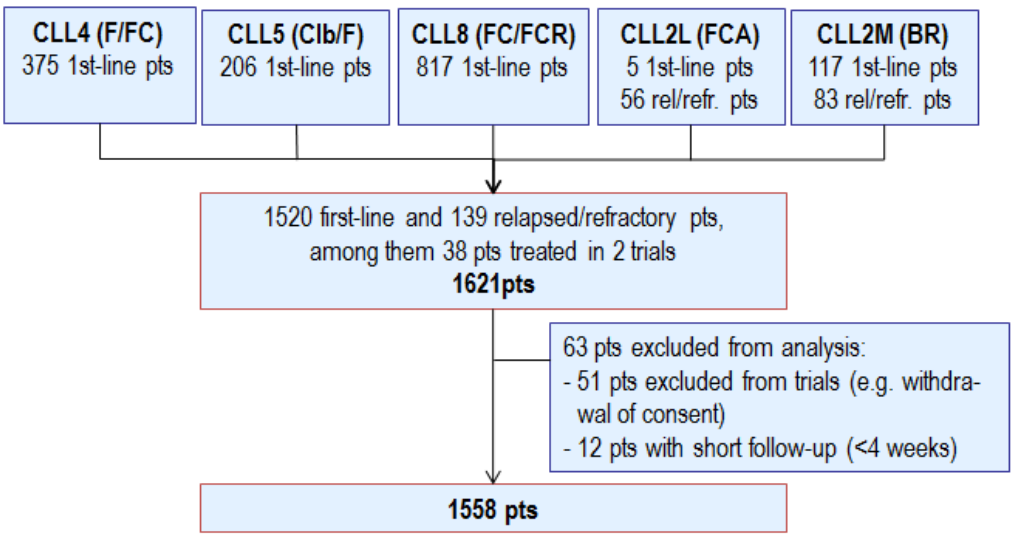
OUTCOME OF ADVANCED CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWING DIFFERENT FIRSTLINE- AND RELAPSE-THERAPIES: A METAANALYSIS OF FIVE PROSPECTIVE TRIALS OF THE GERMAN CLL STUDY GROUP (GCLLSG)

Supplemental table 1: Overview of GCLLSG trials included in the analysis:

Trial	Target population	Treatment	Number of pts		Treatment outcomes		
			1st-line	rel/refr.	OR/CR rate	PFS / EFS	OS
CLL8 (Hallek et al., Lancet 2010; Fischer et al., update 2015 submitted) NCT 00281918	treatment naive, physically fit pts (CIRS-Score ≤ 6 and Crea-Cl ≥ 70ml/Min)	FCR vs FC (6x q28d): Fludarabine (F): 25mg/m² i.v., d1-3; Cyclophosphamide (C): 250mg/m² d1-3; Rituximab (R): 375mg/m², d0, cycle 1 and 500mg/m² d1 cycles 2-6.	FCR: 408 pts FC: 409 pts total: 817 pts	-	FCR: 90%, 44% FC: 80%, 22% p=0.001	med. PFS: FCR: 57 months FC: 33 mo. p<0.001	med. OS: FCR: n.r., FC: 86 mo. OS @ 5.9yrs: FCR: 69% FC: 62% p<0.001
CLL4 (Eichhorst et al., Blood 2006) ISRCTN: 75653261	treatment naive pts aged ≤65 years	F vs FC (6x q28d): Fludarabine (F): 25mg/m² i.v., d1-5 (single F) / 30mg/m² i.v. d1-3 (FC); Cyclophosphamide (C): 250mg/m² p.o. d1-3	F: 182 pts FC: 180 pts total: 375 pts	-	FC: 95%, 35% F: 83%, 18% p=0.001, p<0.001	med. PFS: FC: 48 mo. F: 20 mo. p=0.001	OS @ 3yrs: FC: 80% F: 81% n.s.
CLL5 (Eichhorst et al., Blood 2009) ISRCTN: 36294212	treatment naive pts aged 66-80 years	Clb (12 months) vs F (6x q28d): Chlorambucil (Clb): 0.4- 0.8mg/kg d1+d15; Fludarabine (F): 25mg/m² i.v., d1-5	F: 93 pts Clb: 100 pts total: 206 pts	-	F: 72%, 7% Clb: 51%, 0% p=0.003, p=0.011	med. PFS: F: 19 mo. Clb: 18 mo. n.s.	med. OS: F: 46 mo. Clb: 64 mo. n.s.
CLL2M (Fischer et al., J Clin Oncol 2011/2012) NCT 00274989	treatment naive and relapsed/refractory pts, eligible for chemoimmunotherapy	BR (6x q28d): Bendamustine: 90mg/m² d1-2 (1st-line) or 70mg/m² d1-2 (rel/refr.); Rituximab: 375mg/m² d1, cycle 1; 500mg/m², d1 cycles 2-6	117 pts	83 pts	BR (1st-line): 88%, 23% BR (rel/refr.): 59%, 9%	med. EFS: BR 1st-line: 34 mo. BR rel/refr.: 15 mo. (med. FU: 24 mo.)	OS @ 2y: BR 1st-line: 90% median OS: BR (rel/refr.): 34 months
CLL2L (Elter et al., Leukemia 2012) NCT00147901	treatment naive high-risk/ del(17p) & relapsed/refr. pts, eligible f. chemoimmunotherapy	FCA (3-6 cycles): Fludarabine (F): 25mg/m² i.v., d1-3; Cyclophosphamide (C): 200mg/m² i.v. d1-3; Alemtuzumab s.c.: 3mg d-1 cycle1, 10mg d0 cycle1, 30mg d1-3 cycles 1-6.	5 pts	56 pts	FCA: 56%, 11%	med. PFS: 17 mo. med. EFS: 11 mo.	med. OS: 45 mo.
			1520 pts	139 pts			

CR = complete response; EFS = event free survival; med. = median; mo. = months; OR = overall response; OS = overall survival; pts = patients; rel/refr. = relapsed/refractory; yrs = years

Supplemental figure 1: Consort diagram



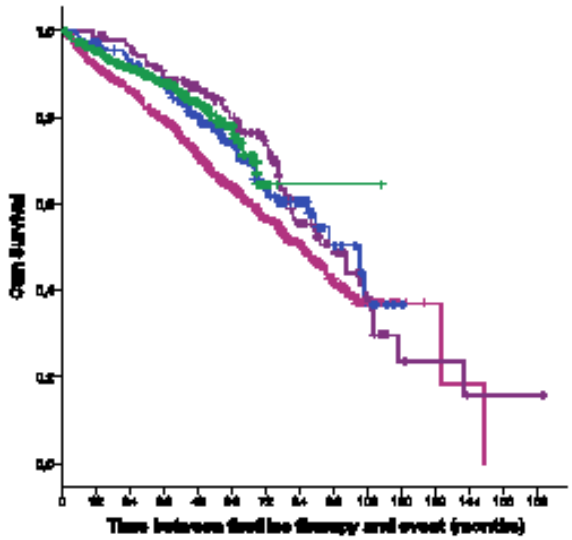
Supplemental table 2: Detailed overview of first-line and relapse therapies

Line of treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
2a) Heterogeneiety of therapies:												
Number of patients	1558	704	392	192	87	37	16	4	2	1	1	1
Number of different therapies	17	60	57	43	32	22	15	4	2	1	1	1
2b) Therapies (absolute number/percentage of patients, 5 most common regimen printed in bold letters):												
Chemoimmunotherapies (1-2 cytotoxic drugs + antibody):												
- fludarabine/cycloph./rituximab (+/-steroids) [FCR]	**402 (25.8%)**	55 (7.8%)	13 (3.3%)	7 (3.6%)	2 (2.3%)	-	-	-	-	-	-	-
- pentostatine/cyclophosphamide/rituximab [PCR]	-	5 (0.7%)	-	-	-	-	-	-	-	-	-	-
- bendamustine/rituximab (+/-steroids) [BR]	**116 (7.4%)**	**75 (10.7%)**	**59 (15.1%)**	**34 (17.7%)**	**7 (8.0%)**	**5 (13.5%)**	-	-	-	-	-	-
- fludarabine/rituximab [FR]	1 (0.1%)	10 (1.4%)	3 (0.8%)	2 (1.0%)	1 (1.1%)	-	-	-	-	-	-	-
- fludarabine/cyclophosphamide/alemtuzumab [FCA]	5 (0.3%)	32 (4.5%)	16 (4.1%)	4 (2.1%)	2 (2.3%)	-	1 (6.3%)	-	-	-	-	-
- fludarabine/cyclophosphamide/ofatumumab [FCO]	-	1 (0.1%)	1 (0.3%)	-	1 (1.1%)	-	-	-	-	-	-	-
- bendamustine/mitoxantrone/rituximab [BMR]	-	3 (0.4%)	1 (0.3%)	-	-	-	-	-	-	-	-	-
- bendamustine/mitoxantrone/alemtuzumab	-	-	1 (0.3%)	-	-	-	-	-	-	-	-	-
- bendamustine/alemtuzumab	-	1 (0.1%)	1 (0.3%)	-	-	-	-	-	-	-	-	-
- fludarabine/alemtuzumab	-	2 (0.3%)	3 (0.8%)	1 (0.5%)	1 (1.1%)	2 (5.4%)	-	-	-	-	-	-
- cyclophosphamide/rituximab (+/- steroids)	-	2 (0.3%)	3 (0.8%)	1 (0.5%)	-	-	-	-	-	-	-	-
- chlorambucil/rituximab (+/- steroids)	-	-	1 (0.3%)	1 (0.5%)	1 (1.1%)	-	-	-	-	-	-	-
Antibody therapies:												
- rituximab (+/- steroids)	-	14 (2.0%)	**21 (5.4%)**	9 (4.7%)	5 (5.7%)	**3 (8.1%)**	1 (6.3%)	1	-	-	-	-
- alemtuzumab (+/- steroids)	-	43 (6.1%)	**24 (6.1%)**	**24 (12.5%)**	**8 (9.2%)**	1 (2.7%)	1 (6.3%)	-	-	-	-	-
- alemtuzumab + rituximab	-	2 (0.3%)	-	-	-	-	-	-	-	-	-	-
- ofatumumab	-	-	-	-	-	-	-	1	-	-	-	-
Single agent chemotherapies:												
- chlorambucil +/- steroids	**134 (8.6%)**	55 (7.8%)	17 (4.3%)	5 (2.6%)	**9 (10.3%)**	1 (2.7%)	**2 (12.5%)**	-	-	-	-	-
- fludarabine +/- steroids [F]	**299 (19.2%)**	**65 (9.2%)**	**21 (5.4%)**	5 (2.6%)	3 (3.4%)	1 (2.7%)	-	-	-	-	-	-
- bendamustine +/- steroids [B]	1 (0.1%)	**63 (9.0%)**	**43 (11.0%)**	**14 (7.3%)**	**7 (8.0%)**	**4 (10.8%)**	1 (6.3%)	-	1	-	-	-
- cyclophosphamide +/- steroids	1 (0.1%)	6 (0.9%)	7 (1.8%)	2 (1.0%)	1 (1.1%)	1 (2.7%)	-	-	-	-	-	-
- vincristine/steroids	-	1 (0.1%)	-	-	1 (1.1%)	1 (2.7%)	-	-	-	-	-	-
- trophosphamide	-	1 (0.1%)	-	2 (1.0%)	-	-	-	-	-	-	-	-
- daunorubicine	-	-	1 (0.3%)	-	-	-	-	-	-	-	-	-

Combined chemotherapies (2 cytotoxic drugs):												
- fludarabine/cyclophspamide [FC]	**588 (37.7%)**	**79 (11.2%)**	**31 (7.9%)**	7 (3.6%)	4 (4.6%)	2 (5.4%)	1 (6.3%)	-	-	-	-	-
- bendamustine/mitoxantrone +/- steroids	-	8 (1.1%)	5 (1.3%)	-	-	-	-	-	-	-	-	-
- bendamustine/etoposide	-	1 (0.1%)	1 (0.3%)	2 (1.0%)	1 (1.1%)	-	-	-	-	-	-	-
- bleomycin/vincristine/steroids [BOP]	-	2 (0.3%)	1 (0.3%)	-	-	-	-	-	-	-	-	-
- chlorambucil/mitoxantrone +/- steroids	2 (0.1%)	-	-	-	-	-	-	-	-	-	-	-
- melphalane/chlorambucil/prednisone [MCP]	-	2 (0.3%)	-	1 (0.5%)	-	-	-	-	-	-	-	-
- vincristine/doxorubicine/steroids [VAD]	-	1 (0.1%)	1 (0.3%)	-	-	-	1 (6.3%)	-	-	-	-	-
Combined chemo(immuno)therapies (>2 cytotoxic drugs +/- antibody):												
- fludarabine/cyclophosphamide/mitoxantrone [FCM]	-	24 (3.4%)	-	1 (0.5%)	-	-	-	-	-	-	-	-
- fludadabine/cycloph./mitoxantr./rituximab [FCMR]	-	2 (0.3%)	1 (0.3%)	3 (1.6%)	-	1 (2.7%)	-	-	-	-	-	-
- ABVD[1] +/- rituximab	-	1 (0.1%)	1 (0.3%)	-	-	-	-	-	-	-	-	-
- Dexa-BEAM[2]	1 (0.1%)	6 (0.9%)	5 (1.3%)	2 (1.0%)	1 (1.1%)	-	-	-	-	-	-	-
- DHA(P)[3] +/- rituximab	-	1 (0.1%)	6 (1.5%)	2 (1.0%)	1 (1.1%)	1 (2.7%)	-	-	-	-	-	-
(R-)CHOP[4] and related therapies:												
- R-CHO(P), Mini-R-CHO(P)	1 (0.1%)	**59 (8.4%)**	**21 (5.4%)**	**13 (6.8%)**	**10 (11.5%)**	1 (2.7%)	**2 (12.5%)**	-	-	-	-	-
- R-COP	-	2 (0.3%)	-	-	-	2 (5.4%)	-	-	-	-	-	-
- CHO(P), Mini-CHO(P)	3 (0.2%)	29 (4.1%)	**21 (5.4%)**	**11 (5.7%)**	5 (5.7%)	1 (2.7%)	**2 (12.5%)**	1	-	-	-	-
- COP	2 (0.1%)	12 (1.7%)	11 (2.8%)	4 (2.1%)	-	1 (2.7%)	-	-	-	-	-	-
Other:												
- lenalidomide	-	-	1 (0.3%)	2 (1.0%)	1 (1.1%)	-	-	-	-	-	-	1
- experimental drugs (in phase-I-trials)	-	8 (1.1%)	4 (1.0%)	2 (1.0%)	1 (1.1%)	2 (5.4%)	-	1	1	-	1	-
- irradiation	-	5 (0.7%)	6 (1.5%)	4 (2.1%)	1 (1.1%)	2 (5.4%)	1 (6.3%)	-	-	-	-	-
- splenectomy	-	2 (0.3%)	1 (0.3%)	-	-	-	-	-	-	-	-	-
Stem cell transplantations (SCT):												
- allogeneic SCT	-	8 (1.1%)	20 (5.1%)	11 (5.7%)	**8 (9.2%)**	**3 (8.1%)**	1 (6.3%)	-	-	-	-	-
- autologous SCT	-	3 (0.4%)	7 (1.8%)	3 (1.6%)	2 (2.3%)	-	-	-	-	-	-	-
- unknown type	-	3 (0.4%)	1 (0.2%)	3 (1.6%)	-	-	-	-	-	-	-	-
- Donor lymphocyte infusion	-	-	2 (0.5%)	3 (1.6%)	2 (2.3%)	-	1 (6.3%)	-	-	-	-	-
Therapies not listed as administered in 1 pt. only	2 (0.1%)	10 (1.4%)	8 (2.0%)	7 (3.6%)	1 (1.1%)	2 (5.4%)	1 (6.3%)	-	-	1	-	-

[1] ABVD: doxorubicine, bleomycin, vinblastin, dacarbazine
[2] Dexa-BEAM: dexamethasone, BCNU, etoposide, cytarabine, melphalane
[3] (R-)DHAP: (rituximab), dexamethasone, cytarabine, (cisplatin)
[4] (R-)CHO(P): (rituximab), cyclophosphamide, doxorubicine, vincristine (+/- steroids); (R-)COP: (rituximab), cyclophosphamide, doxorubicine, steroids

Supplemental figure 2:
Impact of anti-CD20 antibody-treatment on overall survival time



pts receiving an anti-CD20 antibody-containing regimen for 1st-line treatment* [median OS: n.r.]
pts receiving an anti-CD20 antibody-containing regimen for 2nd-line treatment* [med. OS: 105.2 mo.]
pts receiving an anti-CD20 antibody-containing regimen for ≥3rd-line treatment* [med. OS: 96.7 mo.]
pts never receiving an anti-CD20 antibody [med. OS 85.5 mo.]

*) and eventually later

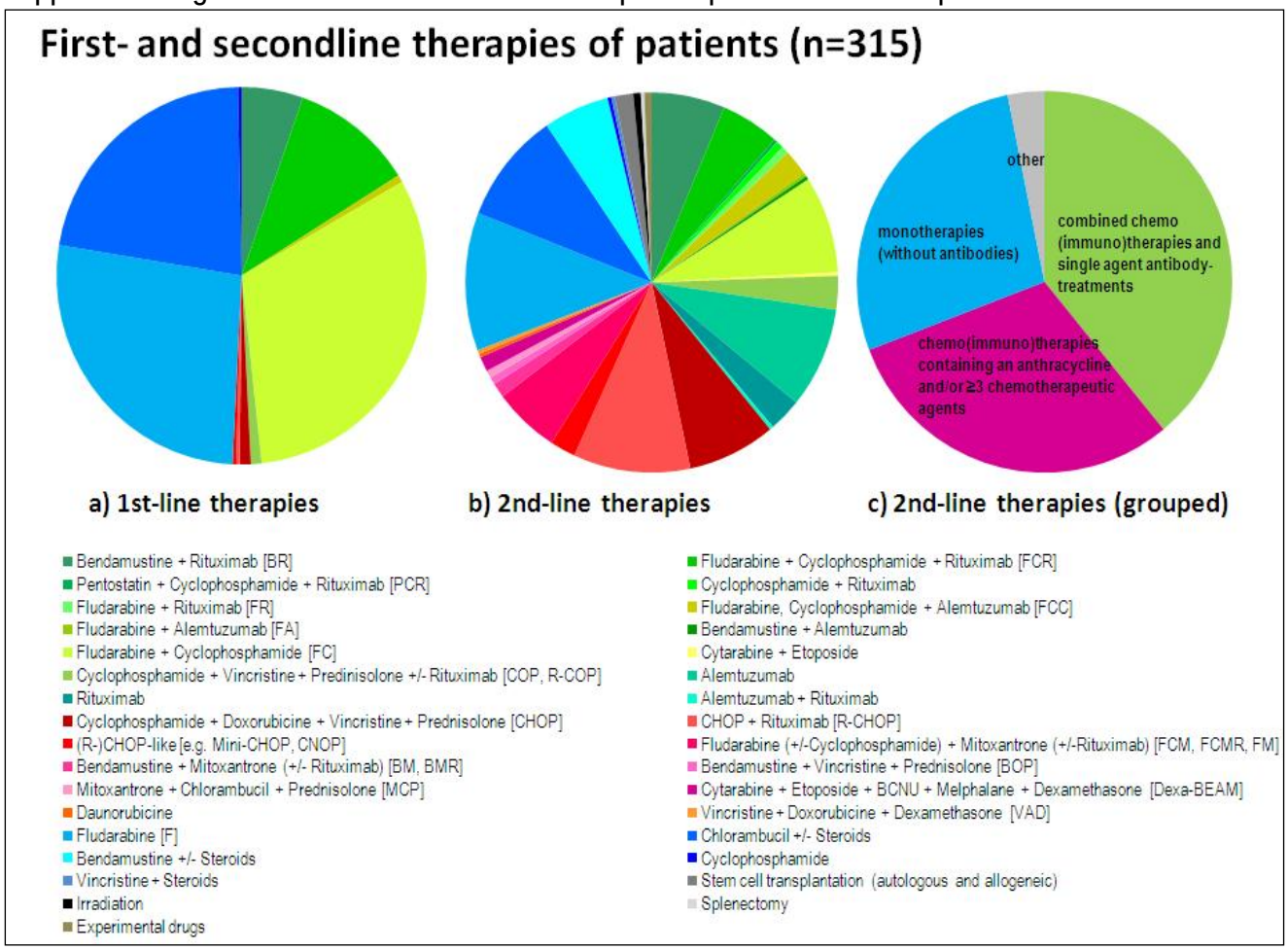
Supplemental table 3: Use of (R-)CHOP(-like) therapies and subsequent regimen:

Use of (R-)CHOP(-like) therapies		Therapies administered after (R-)CHOP(-like) therapy
Treatment-line	No. of pts	Regimen and no. of pts
1st-line	7 (3.1%)	CLBP (1x), FC (1x), CAM (2x), BR (1x), FCC (1x), F (1x)
2nd-line	106 (46.9%)	F (3x), R (2x), CHOP (4x), B (3x), AutoTx (4x), BR (9x), RadTx (2x), R-CLB (1x), DHAP (2x), CAM (4x), R-Doxo (1x), B-Cam (1x), BM (1x), Carbo/Paclitaxel (1x), R-DHAP (2x), AlloTx (2x), R-FCM (1x), Dex-Cam (1x), Experimental (1x), R-ICE (1x), CLB (1x), COP (5x), FC (1x), Cyclophosphamide (1x)
3rd-line	58 (25.7%)	CLB (2x), DHAP (1x), CHOP (1x), AlloTX (2x), B (1x), R-Vino (1x), BR (3x), Cam (5x), CLBP (1x), AutoTX (1), RadTx (1x), Experimental (1x), R-Cyclophoasphamide (1x), RCHOP (2x), F (1x), COP (1x), BP (1x), R-DHAP (1x), FCam (1x)
4th-line	30 (13.3%)	Cam (2x), CHOP (2x), Cyclophosphamide (1x), CLBP (2x), CLB (1x), R-DHAP (1x), FCCam (1x), AlloTx (1x), BR (2x), B (1x), FC-Ofatumumab (1x)
5th-line	15 (6.6%)	BP (1x), Cyclophosphamide (1x), Experimental (1x), BR (1x)
6th-line	5 (2.2%)	FCCam (1x), CLBP (1x), VAD (1x)
7th-line	4 (1.8%)	CHOP (1x), Experimental (1x)
8th-line	1 (0.4)	-
Total	226	

Supplemental table 4: Repetition of treatment and subsequent regimen:

Repeated regimen		Subsequent therapies
Treatment-line	Regimen and no of pts	Regimen and no of pts
1+2	BR (1x)	-
	CLB (14x)	CLB (2x), F (4x)
	CLBP (2x)	F (2x)
	F (18x)	B (2x), BR (2x), Cam (1x), CHOP (1x), CLB (1x), CLBP (1x), F (1x), FCR (1x), FR (1x)
	FC (25x)	B (4x), BM-Cam (1x), BP (1x), BR (2x), RCHOP (1x), R-AraDex (1x), FC (1x), FCCam (1x), FCR (2x), MCHOP (1x), R-CLBP-M (1x), R (1x)
	FCR (11x)	R-OP (1x), Cam (1x), FCR (1x)
2+3	B (8x)	B (1x)
	B-Eto (1x)	BR (1x)
	BM (1x)	B (1x)
	BP (1x)	-
	BR (3x)	AlloTx (1x)
	Cam (5x)	BR (2x), AlloTx (1x)
	CHOP (3x)	CHOP (1x), CLB (1x)
	CLB (2x)	F (1x)
	COP (4x)	BR (1x), F (1x)
	F (4x)	Cam (1x), F (1x)
	FC (7x)	BR (2x)
	FCR (2x)	R (1x)
	R (1x)	-
	RadioTx (1x)	-
3+4	B (1x)	-
	B-Eto (1x)	-
	BR (2x)	-
	Cam (1x)	AlloTx (1x)
	Dex-Cam (1x)	RCHOP (1x)
	CHOP (1x)	CHOP (1x)
	CLB (1x)	CLB (1x)
	COP (1x)	FC-Ofatumumab (1x)
	F(1x)	R-CHOP (1x)
	FC (1x)	FC/RCHOP (1x)
4+5	BR (1x)	-
	Cam (1x)	-
	CHOP (1x)	BP (1x)
	CLB (1x)	B (1x)
	R-CLBP (1x)	-
5+6	-	-
6+7	B (1x)	-
7+8	R (1x)	-
Total	132	

Supplemental figure 3: First- and second-line therapies of patients with a relapse <24 months:



Supplemental table 5: Impact of regimen used for 2nd-line <24 months after 1st-line therapy (n=315):

Regimen	Number of pts [n, %]	Median TFS [months]	Median OS [months]
3a) Impact of the ten most prevalent regimen for 2nd-line <24 months after 1st-line:			
R-CHOP	32 (10.2%)	9.1	30.2
CHOP	24 (7.6%)	6.9	41.3
FCM	16 (5.1%)	29.0	49.2
Alemtuzumab	27 (8.6%)	18.6	49.6
FC	26 (8.3%)	30.8	88.4
FCR	16 (5.1%)	16.0	62.1
BR	15 (4.8%)	20.0	n.r.
F	37 (11.7%)	12.7	49.3
Clb	21 (6.7%)	7.3	109.3
B	15 (4.8%)	16.4	44.8
3b) Impact of different drugs used for 2nd-line <24 months after 1st-line:			
with/without antibody	87 / 136	15.5 vs. 15.3	51.2 vs. 53.7
with/without rituximab	61 / 162	15.3 vs. 16.0	51.2 vs. 53.7
with/without alemtuzumab	27 / 196	18.6 vs. 15.3	49.6 vs. 52.4
With/without bendamustine	33 / 190	20.0 vs. 15.1	53.9 vs. 52.4
CHOP(-like) yes/no	54 / 169	8.2 vs 16.8 (p<0.0001)	35.5 vs. 61.0 (p=0.007)
R-CHOP(-like) yes/no	31 / 169	9.1 vs. 16.7 (p=0.013)	30.2 vs. 61.0 (p=0.052)