

1 **Supplemental Material**
 2 **Table S1. Patients with Richter's transformation**
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Patient #	Time from Richter's transformation to CAR-T cell infusion (months)	Regimens initiated after Richter's transformation
CLL-ibru-1	3	Nivolumab Venetoclax
CLL-ibru-5	42	R-EPOCH Acalabrutinib+obinutuzumab Ibrutinib Nivolumab Radiotherapy of cervical lymphadenopathy
CLL-ibru-7	42	R-CHOP Radiotherapy of left axillary lymphadenopathy Ibrutinib Venetoclax
CLL-ibru-19	7	R-CHOP Venetoclax Ibrutinib

4 Abbreviations: CAR-T cell, chimeric antigen receptor-engineered T cell; R-EPOCH, rituximab,
 5 etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicine; R-CHOP, rituximax,
 6 cyclophosphamide, doxorubicine, vincristine, prednisolone.
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9 **Table S2. Response at 4 weeks after CD19 CAR-T cell therapy with concurrent**
 10 **ibrutinib**

	N* (%)
Response by 2018 iwCLL criteria	
ORR (CRi + PR)	15/18 (83)
CRi	4/18 (22)
PR	11/18 (61)
SD	0/18 (0)
PD	3/18 (17)
Nodal response by 2018 iwCLL CT criteria§	
ORR (CR + PR)	10/14 (71)
CR	1/14 (7)
PR	9/14 (64)
SD	1/14 (7)
PD	3/14 (22)
Marrow response	
No detectable disease by flow cytometry (sensitivity: 10 ⁻⁴)	13/18 (72)
No detectable disease by <i>IGH</i> sequencing (sensitivity: 10 ⁻⁶)	11/18 (61)

11 *One patient died at day 4 after CAR-T cell infusion and was not evaluable for response.

12 §Fourteen of 16 patients with measurable nodal disease before lymphodepletion were
 13 evaluable for IWCLL CT response (early death, n=1; CT not performed at restaging, n=1)

14 Abbreviations: CAR-T cell, chimeric antigen receptor-engineered T cell; iwCLL,
 15 International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rates;
 16 CRi, complete response with incomplete hematologic recovery, PR, partial response, SD,
 17 stable disease, PD, progressive disease, CT, computed tomography

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Table S3. Causes and timing of ibrutinib dose reduction or discontinuation after CD19 CAR-T cell therapy with concurrent ibrutinib

Patient #	Cause of first ibrutinib dose reduction or discontinuation	Day of first ibrutinib dose reduction or discontinuation*	Total duration of concurrent ibrutinib therapy (days)*
CLL-ibru-3	Disease progression	84	84
CLL-ibru-5	Grade 3 neurologic toxicity	4	25
CLL-ibru-6	Grade 3 thrombocytopenia§	7	89
CLL-ibru-14	Grade 3 neurologic toxicity	21	24
CLL-ibru-16	Disseminated intravascular coagulation during grade 2 CRS	6	6
CLL-ibru-18	Microembolic strokes in the context of DIC during grade 3 neurologic toxicity	8	8
CLL-ibru-15	Sudden death from presumed cardiac arrhythmia during grade 2 CRS not requiring vasopressors	NA	4

23 *After CAR-T cell infusion §CLL-ibru-6 continued on ibrutinib at a reduced dose.

24 Abbreviations: CAR-T cell, chimeric antigen receptor-engineered T cell; CRS, cytokine
25 release syndrome; DIC, disseminated intravascular coagulation.

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28 **Table S4. Grade 3-4 adverse events according to CTCAE 4.03 after CD19 CAR-T**
 29 **cell therapy with concurrent ibrutinib**
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Adverse event	N	%
Neutropenia	19	100
Lymphopenia	19	100
Anemia	15	79
Thrombocytopenia	13	68
Hypertension	7	37
Hypophosphatemia	5	26
Hyponatremia	4	21
Hyperglycemia	4	21
Elevated ALT	2	11
Thromboembolic event	2	11
Muscle weakness	2	11
Elevated AST	2	11

31 *occurring in >10% of patients. Abbreviations: CTCAE, Common Terminology Criteria for
 32 Adverse Events; CAR-T cell, chimeric antigen receptor-engineered T cell; ALT, alanine
 33 transaminase; AST, aspartate transaminase.

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36 **Table S5. Comparison of baseline characteristics between the Con-ibr and the**
 37 **No-ibr cohort**

	Con-ibr cohort	No-ibr cohort	p
	n = 19	n = 19	
Age (years – median [IQR])	65 [56 – 69]	61 [53 – 64]	0.24
Female gender (n – (%))	7 (37)	9 (37)	1
ECOG performance status 1 (n – (%))	9 (47)	9 (47)	1
Richter’s transformation (n – (%))	4 (21)	4 (21)	1
17p deletion (n – (%))	14 (74)	12 (63)	0.73
11q abnormality (n – (%))	5 (26)	9 (50)	0.18
Complex karyotype* (n – (%))	14 (74)	16 (89)	0.40
Cross-sectional tumor area† (mm ² – median [IQR])	1,538 [840 – 3,959]	3,229 [2428 – 5562]	0.04
Bulky disease (largest node ≥ 5 cm, [n – (%)])	4 (21)	6 (32)	0.71
Serum LDH concentration (units/L – median [IQR])	155 [135 – 206]	225 [196 – 356]	0.009
Blood absolute lymphocyte count (10 ⁹ cells/L – median [IQR])	1.12 [0.84 – 3.95]	1.66 [0.93 – 8.38]	0.46
Blood CLL cell count (10 ⁹ cells/L – median [IQR])	0.45 [0.13 – 3.13]	1.25 [0.04 – 6.56]	0.92
Marrow CLL burden			
Immunohistochemistry (bone marrow biopsy, % cellularity) Median [IQR])	35 [9 – 70]	60 [35 – 72]	0.54
Flow cytometry (bone marrow aspirate, % of leukocytes) Median [IQR])	26 [12 – 60]	59 [28 – 77]	0.23
Prior therapies (number – median [IQR])	5 [4 – 7]	5 [4 – 5]	0.19
Prior stem cell transplantation (n – (%))	3 (16)	3 (16)	1
Prior treatment with FCR	11 (58)	11 (58)	1
Prior treatment with venetoclax (n – (%))	11 (58)	5 (26)	0.10
Duration of last treatment with ibrutinib prior to leukapheresis (days – median [IQR])	105 [26 – 741]	398 [200 – 649]	0.26
CyFlu lymphodepletion (n – (%))	19 (100)‡	19 (100)§	1

38 *Defined as ≥3 chromosomal abnormalities. †In patients with evaluable nodal disease. ‡Cy dose
 39 in the Con-ibr cohort was 300mg/m²/day for 3 days in all 19 patients; Flu dose was as follows:
 40 30mg/m²/day for 3 days (n=18), 20mg/m²/day for 3 days (n=1). §Cy dose in the No-ibr was as
 41 follows: 300mg/m²/day for 3 days (n=5), 500mg/m²/day for 3 days (n=2), 30mg/kg/day for 1 day
 42 (n=1), 60mg/kg/day for 1 day (n=11); Flu dose in the No-ibr cohort was as follows: 25mg/m²/day
 43 for 3 days (n=12), 30mg/m²/day for 3 days (n=7). All variables were assessed prior to
 44 lymphodepletion chemotherapy, unless specified. Two-sided p values per Wilcoxon Sum Rank
 45 test or Fisher’s test, as appropriate. Abbreviations: Con-ibr, concurrent ibrutinib; No-ibr, ibrutinib
 46 discontinued prior to lymphodepletion; IQR, interquartile range, ECOG, eastern cooperative
 47 oncology group; SUV, standardized uptake value, LDH, lactate dehydrogenase; CLL, chronic
 48 lymphocytic leukemia, CAR-T cell, chimeric antigen receptor-engineered T cells; FCR,
 49 fludarabine, cyclophosphamide, rituximab.

50 **Table S6. Proportional odds model to predict the grade of CRS**
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Predictors	Adjusted OR*	95% CI	p
Cohort			
No-ibr	1		
Con-ibr	0.25	0.06 – 0.99	0.05
Marrow CLL burden (%)	3.44	0.97 – 12.22	0.06
LDH serum concentration (units/L)	0.97	0.69 – 1.36	0.86
Cross-sectional tumor area (mm ²)	0.87	0.37 – 2.01	0.75

52 Abbreviations: Con-ibr, concurrent ibrutinib; No-ibr, ibrutinib discontinued prior to
 53 lymphodepletion; OR, odds ratio; CI, confidence interval; CLL, chronic lymphocytic
 54 leukemia; CAR-T cell, chimeric antigen receptor-engineered T cells; LDH, lactate
 55 dehydrogenase. Confidence intervals and p values per Wald test.

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57 **Table S7. CAR-T cell end-manufacturing product characteristics in the Con-ibr**
 58 **cohort compared to the No-ibr cohort**

	Con-ibr (n=19)	No-ibr (n=19)	p*
CD4+ subset			
T cell population doublings† after anti-CD3/CD28 bead stimulation (median [IQR])	2.72 [2.47, 3.34]	3.02 [2.82, 3.29]	0.64
CAR-T cell population doublings† after LCL stimulation (median [IQR])	7.71 [7.33, 8.24]	7.90 [7.35, 8.04]	0.89
CD62L+ (median percentage [IQR])	56.85 [40.70, 68.68]	54.20 [40.75, 61.55]	0.64
Naive (median percentage [IQR])	3.16 [1.24, 10.04]	1.34 [0.30, 3.36]	0.31
Central memory (median percentage [IQR])	49.00 [35.83, 59.58]	55.50 [38.80, 60.80]	0.64
Effector memory (median percentage [IQR])	42.25 [24.52, 55.10]	42.90 [33.00, 57.25]	0.84
Effector memory RA+ (median percentage [IQR])	2.50 [1.38, 4.80]	1.38 [0.12, 3.42]	0.33
CD8+ subset			
T cell population doublings† after anti-CD3/CD28 stimulation (median [IQR])	1.89 [1.24, 2.52]	2.46 [0.43, 3.17]	0.64
CAR-T cell population doublings† after LCL stimulation (median [IQR])	7.97 [7.42, 8.29]	7.75 [6.75, 8.65]	0.67
CD62L+ (median percentage [IQR])	45.85 [33.98, 56.50]	55.60 [40.60, 71.00]	0.54
Naive (median percentage [IQR])	9.09 [2.40, 20.48]	3.20 [0.32, 5.62]	0.3
Central memory (median percentage [IQR])	32.70 [28.85, 58.45]	48.90 [40.75, 57.50]	0.33
Effector memory (median percentage [IQR])	35.75 [21.38, 49.60]	42.90 [30.45, 54.15]	0.56
Effector memory RA+ (median percentage [IQR])	6.71 [1.57, 12.20]	1.29 [0.28, 2.21]	0.09

59 *p values from Wilcoxon Sum Rank test (two-sided) adjusted for multiple comparisons using the Benjamini-Hochberg procedure.
 60 †Population doublings were calculated using the equation $A_t = A_0 \cdot 2^n$, where n is the number of population doublings, A_0 is the input
 61 number of cells before ex vivo stimulation, and A_t is the number of cells after ex vivo stimulation.
 62 Naïve, central memory, and effector memory phenotypes were defined as CD45RA+CD62L+, CD45RA-CD62L+ cells, CD45RA-
 63 CD62L- cells, respectively, in a CD3+/CD4+ or CD8+/EGFRt+ gate. *p values from Wilcoxon Sum Rank test (two-sided) adjusted for
 64 multiple comparisons using the Benjamini-Hochberg procedure.
 65

66 **Table S8. Correlations between peak cytokine serum concentrations and severe**
 67 **(grade ≥ 3) CRS**
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Peak cytokine serum concentration	Somers' Dxy rank correlation index
MCP-1	0.94
IL-6	0.89
IL-8	0.77
IL-2R α	0.71
TIM-3	0.71
IL-10	0.49
sIL-6R	0.49
TNFRp75	0.31
IFN- γ	0.26
sFAS	0.26
MIP-1b	0.09
TNFRp55	0.03
IL-18	-0.09
IL-7	-0.09
IL-22	-0.14
IL-15	-0.20
TNF- α	-0.60
IL-2	-0.66
IL-5	-0.94
TGF- β	-1.00

69 Cytokines were ranked according to the strength of correlation between the peak cytokine
 70 serum concentrations and grade ≥ 3 CRS using Somers' Dxy rank correlation index.
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72 **Table S9. Comparisons of peak cytokine serum concentrations between the Con-**
 73 **ibr and No-ibr cohorts**
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Peak cytokine serum concentration (pg/mL)	Con-ibr	No-ibr	p*
MCP-1 (median [IQR])	411.38 [197.01, 1124.65]	1738.22 [986.54, 2440.56]	0.018
IL-6 (median [IQR])	25.02 [3.28, 83.47]	53.78 [13.30, 597.62]	0.278
IL-8 (median [IQR])	17.09 [8.99, 94.82]	80.78 [38.51, 227.18]	0.051
IL-2R α (median [IQR])	165.70 [139.53, 637.46]	4469.28 [2106.56, 8751.02]	<0.001
TIM-3 (median [IQR])	10907.52 [5942.44, 17174.36]	20803.06 [10791.04, 29397.90]	0.095
IL-10 (median [IQR])	71.81 [30.22, 298.25]	75.46 [46.12, 212.44]	0.818
siL-6R (median [IQR])	27823.65 [17279.76, 48404.96]	26196.51 [18122.66, 41149.43]	0.802
TNFRp75 (median [IQR])	18602.69 [9309.96, 22734.03]	14969.55 [10965.24, 18876.22]	0.710
IFN γ (median [IQR])	5.75 [2.13, 19.85]	8.21 [0.98, 15.15]	0.911
sFAS (median [IQR])	4876.38 [3232.31, 8098.14]	16538.12 [11651.19, 18826.32]	<0.001
MIP-1b (median [IQR])	378.57 [196.79, 1533.76]	943.10 [544.24, 1357.59]	0.207
TNFRp55 (median [IQR])	8094.09 [3907.61, 12661.85]	13028.40 [10554.32, 17100.20]	0.096
IL-18 (median [IQR])	2458.93 [1240.49, 3574.19]	5139.71 [3316.89, 7070.55]	0.018
IL-7 (median [IQR])	15.24 [10.42, 23.12]	31.50 [15.97, 37.24]	0.086
IL-22 (median [IQR])	72.29 [72.29, 72.29]	72.29 [72.29, 72.29]	0.589
IL-15 (median [IQR])	37.39 [30.10, 64.59]	99.42 [55.03, 146.64]	0.005
TNF- α (median [IQR])	1.89 [1.32, 6.32]	4.22 [1.32, 30.83]	0.348
IL-2 (median [IQR])	3.43 [3.43, 3.43]	3.43 [2.12, 5.18]	0.798
IL-5 (median [IQR])	6.96 [6.96, 6.96]	10.82 [5.47, 23.21]	0.315
TGF- β (median [IQR])	64076.22 [48111.76, 97389.70]	68977.58 [48462.86, 109011.36]	1.000

75 *p values from Wilcoxon Sum Rank test (two-sided) adjusted for multiple comparisons using the Benjamini-
 76 Hochberg procedure. Abbreviations: Con-ibr, concurrent ibrutinib; No-ibr, ibrutinib discontinued prior to
 77 lymphodepletion; IQR, interquartile range
 78

79 **Table S10. CAR-T cell end-manufacturing product characteristics according to**
 80 **the 4-week iwCLL response after CAR-T cell therapy with or without concurrent**
 81 **ibrutinib**

	4-week response (2018 iwCLL criteria)		p*
	CRi/PR (n=11)	SD/PD (n=25)	
CD4+ subset			
T cell population doublings† after bead stimulation (median [IQR])	2.87 [2.51, 3.34]	3.02 [2.81, 3.24]	0.96
CAR-T cell population doublings† after LCL stimulation (median [IQR])	7.83 [7.22, 8.24]	7.64 [7.37, 8.03]	0.96
CD62L+ (median percentage [IQR])	53.55 [40.55, 68.62]	56.00 [40.75, 62.15]	0.96
Naive (median percentage [IQR])	2.26 [1.09, 8.76]	0.43 [0.19, 2.67]	0.96
Central memory (median percentage [IQR])	51.40 [35.12, 59.85]	49.30 [40.75, 60.85]	0.96
Effector memory (median percentage [IQR])	42.05 [28.58, 58.23]	45.30 [33.30, 53.65]	0.96
Effector memory RA+ (median percentage [IQR])	2.12 [0.94, 4.23]	0.52 [0.13, 3.83]	0.96
CD8+ subset			
T cell population doubling† after anti-CD3/CD8 bead stimulation (median [IQR])	2.39 [1.73, 2.69]	1.89 [0.26, 3.14]	0.96
CAR-T cell population doublings after LCL stimulation (median [IQR])	7.89 [7.23, 8.41]	7.96 [6.75, 8.61]	0.96
CD62L+ (median percentage [IQR])	54.70 [44.22, 60.73]	39.20 [34.20, 74.25]	0.96
Naive (median percentage [IQR])	4.85 [1.23, 14.07]	3.87 [0.39, 5.62]	0.96
Central memory (median percentage [IQR])	47.75 [31.93, 58.50]	39.70 [31.50, 54.70]	0.96
Effector memory (median percentage [IQR])	37.80 [28.88, 43.70]	49.90 [26.65, 60.15]	0.96
Effector memory RA+ (median percentage [IQR])	2.50 [0.94, 8.14]	1.68 [0.57, 4.58]	0.96

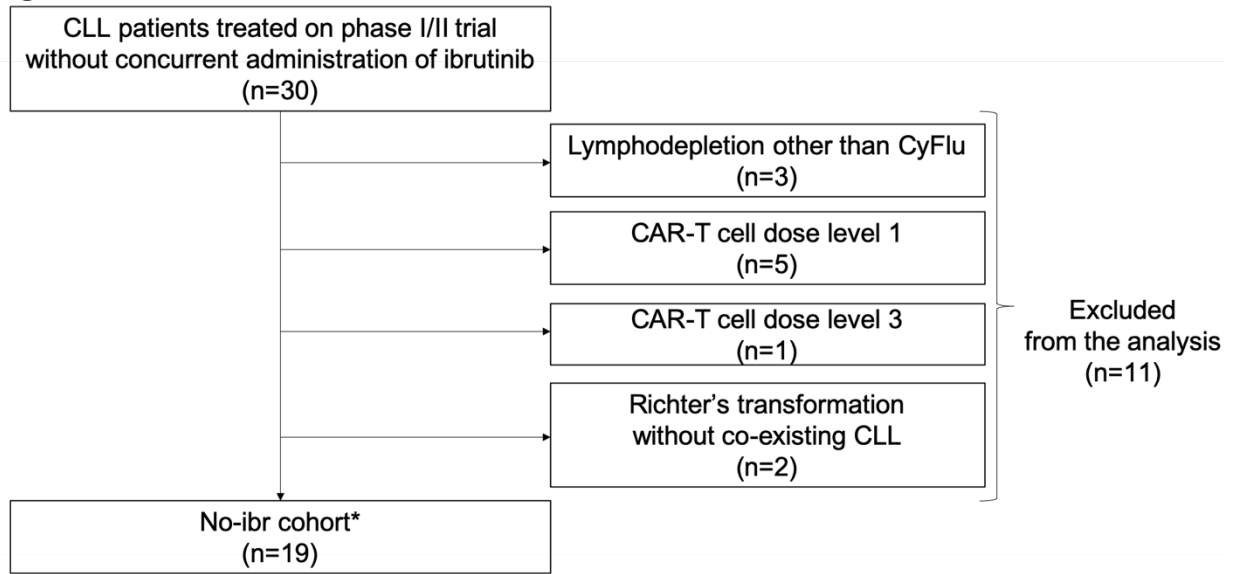
*p values from Wilcoxon Sum Rank test (two-sided) adjusted for multiple comparisons using the Benjamini-Hochberg procedure.

†Population doublings were calculated using the equation $A_t = A_0 \cdot 2^n$, where n is the number of population doublings, A_0 is the input number of cells before ex vivo stimulation, and A_t is the number of cells after ex vivo stimulation.

Naïve, central memory, and effector memory phenotypes were defined as CD45RA+CD62L+, CD45RA-CD62L+ cells, CD45RA-CD62L- cells, respectively, in a CD3+/CD4+ or CD8+/EGFRt+ gate. *p values from Wilcoxon Sum Rank test (two-sided) adjusted for multiple comparisons using the Benjamini-Hochberg procedure.

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89 **Figure S1. Patient selection for the No-ibr cohort**

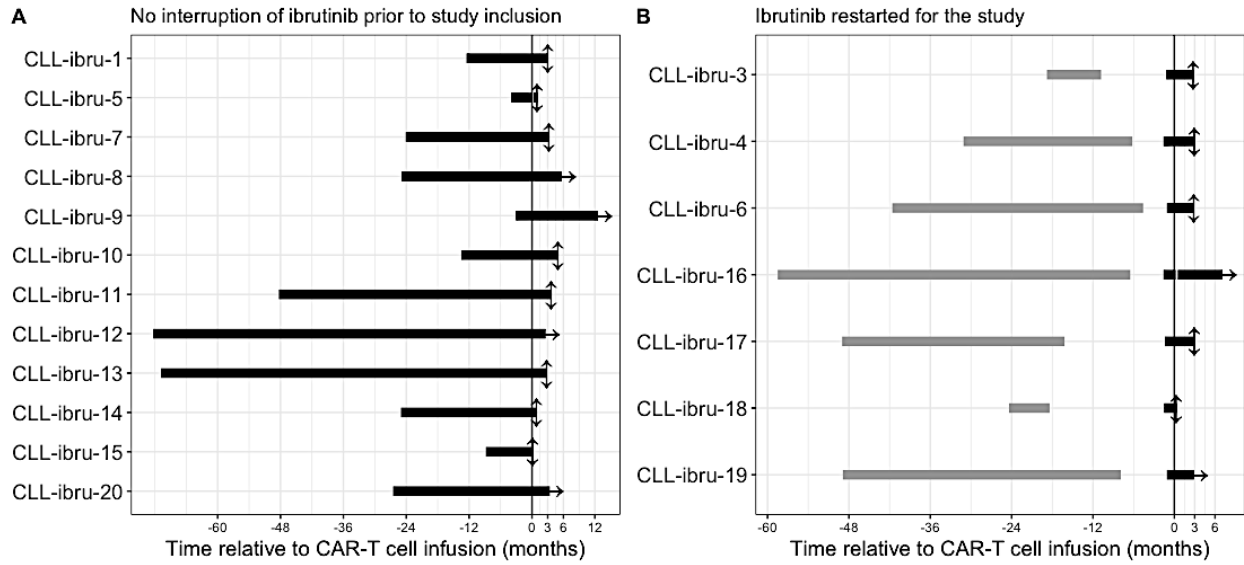


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91 *14 of these patients were included in a previous report⁸.

92 Abbreviations: CLL, chronic lymphocytic leukemia; CyFlu, cyclophosphamide and
93 fludarabine lymphodepletion; CAR-T cell, chimeric antigen receptor-engineered T cell.

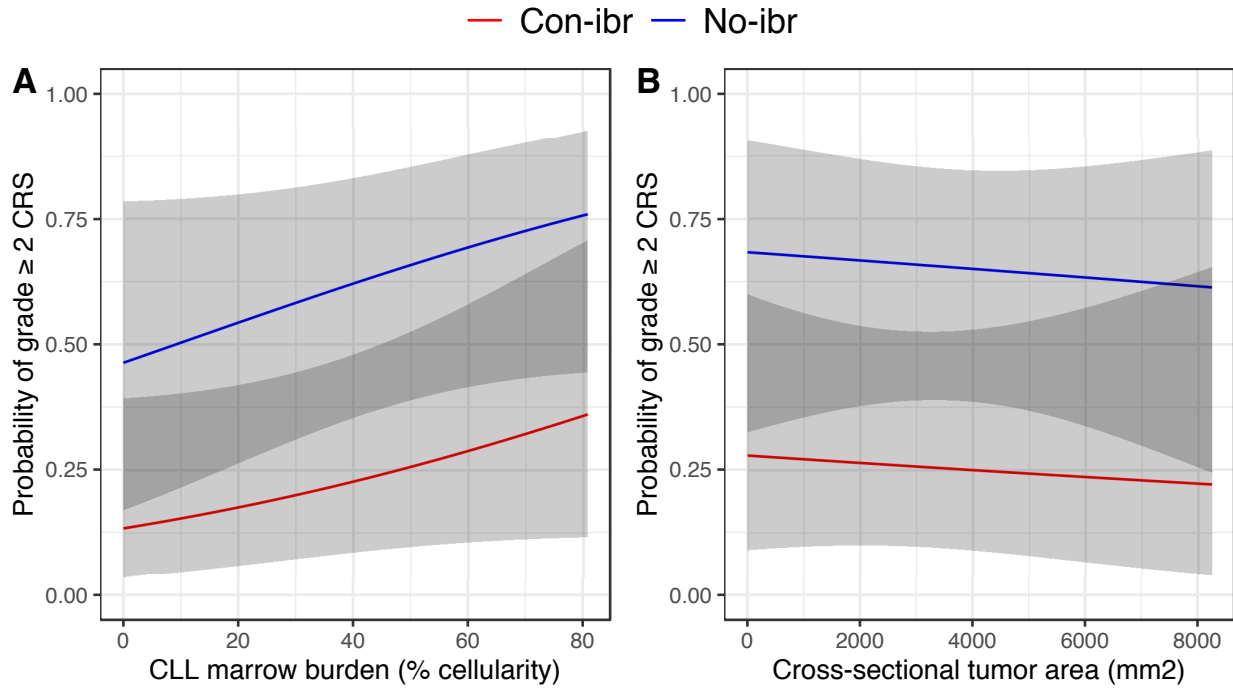
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96 **Figure S2. Ibrutinib exposure in study participants**
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 99 Each horizontal bar symbolizes the timing and duration of ibrutinib therapy prior to and
 100 during study for a single patient. Only the last ibrutinib treatment prior to study
 101 participation is shown. Vertical lines represent the time of CAR-T cell infusion. Double
 102 arrows, discontinuation of ibrutinib; single arrow, continuation of ibrutinib at last follow-up.
 103

104 **Figure S3. Concurrent ibrutinib was independently associated with lower CRS**
105 **severity after adjusting for disease burden**



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107 Predicted probabilities of grade ≥ 2 CRS in the Con-ibr (red line) and No-ibr cohort (blue
108 line) obtained from a proportional odds ordinal regression model (Table S6) using data

109 from all 38 patients. Shaded areas show the 95% confidence intervals of the estimates.

110 In A, predictions were also adjusted for the median CD8+ peak CAR-T cell expansion,

111 the median prelymphodepletion LDH serum concentration, and the median

112 prelymphodepletion cross-sectional tumor area. In B, predictions were also adjusted for

113 the median CD8+ peak CAR-T cell expansion, the median prelymphodepletion LDH

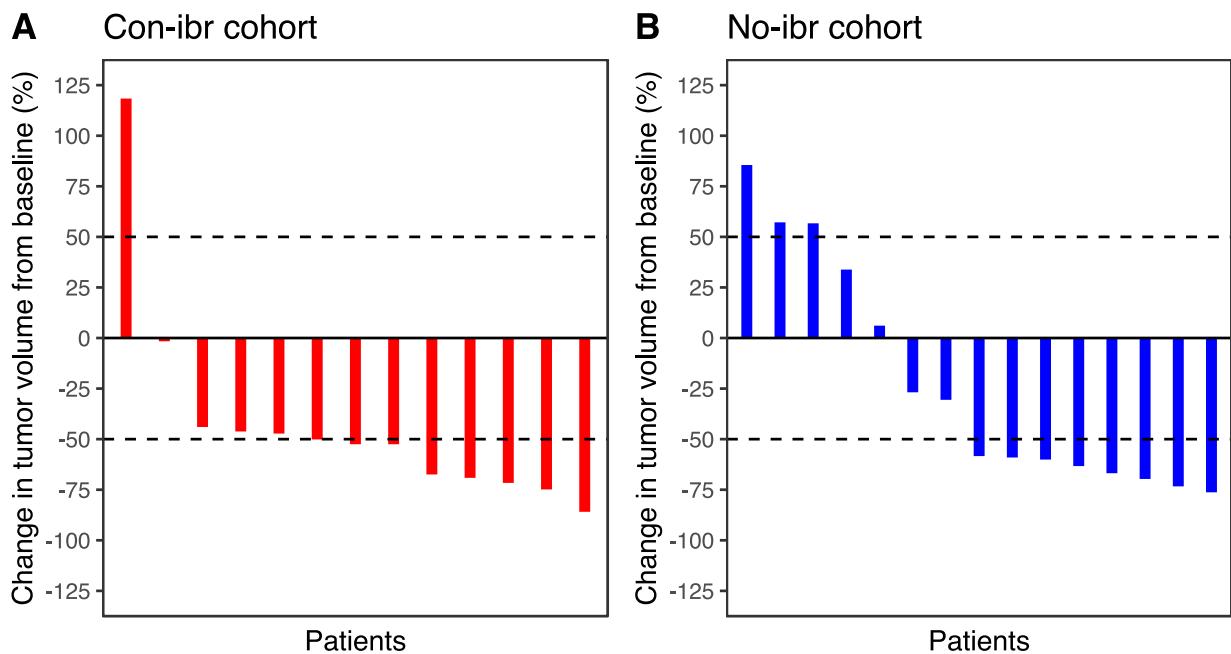
114 serum concentration, and the median CLL marrow burden. Abbreviations: Con-ibr,

115 concurrent ibrutinib; No-ibr, ibrutinib discontinued prior to lymphodepletion; CRS, cytokine

116 release syndrome; CLL, chronic lymphocytic leukemia.

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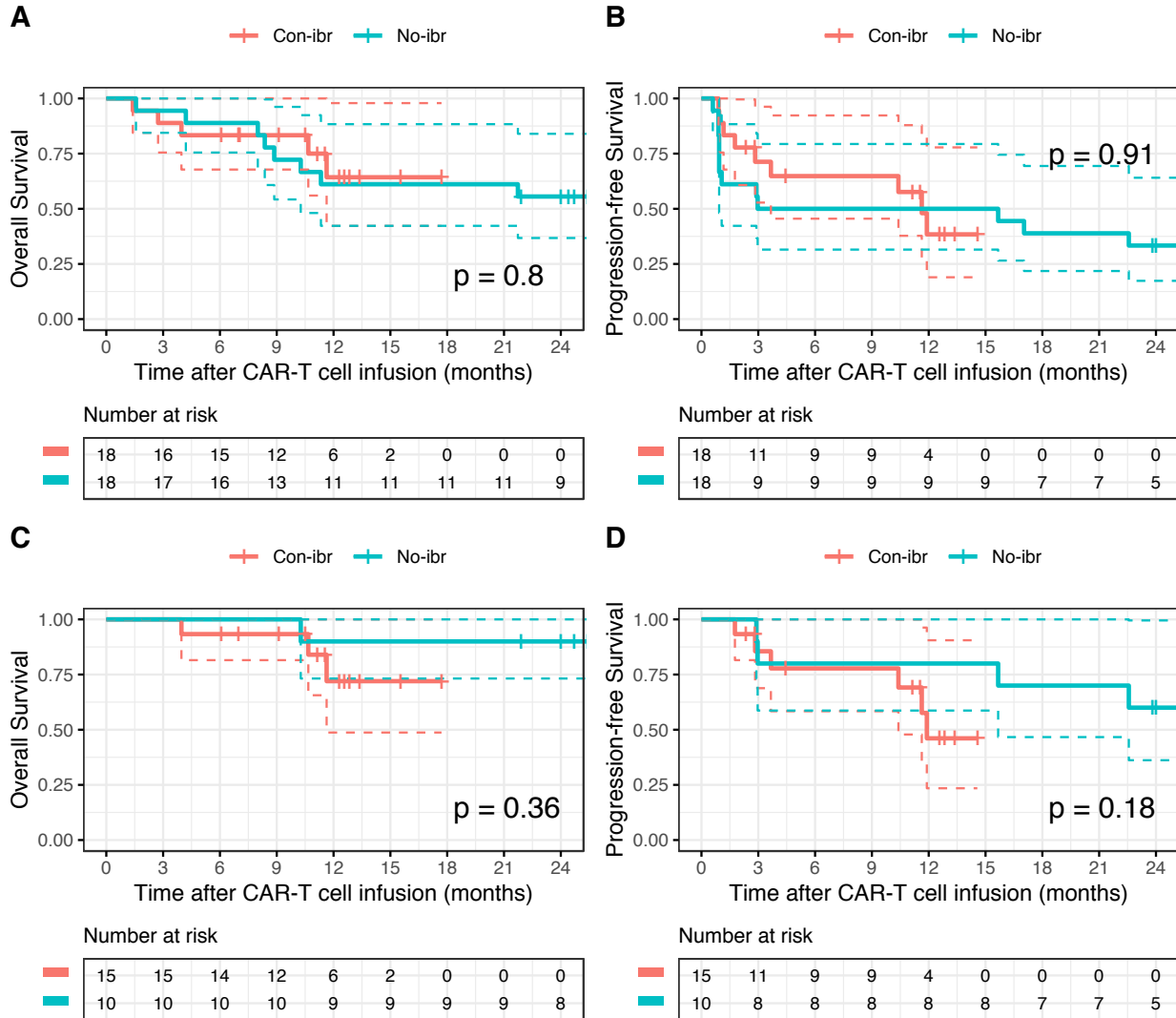
118 **Figure S4. Tumor volume reduction at 4 weeks after CD19 CAR-T cell therapy with**
119 **and without concurrent ibrutinib**



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121 Among patients restaged with CT imaging (Con-ibr, n=14; No-ibr, n=17), no SPD data
122 was available to determine tumor volume change in one patient in the Con-ibr cohort, and
123 in two patients in the No-ibr cohort. Abbreviations: Con-ibr, concurrent ibrutinib; No-ibr,
124 ibrutinib discontinued prior to lymphodepletion; CAR, chimeric antigen receptor.
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Figure S5. Overall and progression-free survival probabilities after CD19 CAR-T cell therapy in CLL patients with and without concurrent ibrutinib



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Solid lines show the Kaplan-Meier estimates in all patients (**A, B**) and in responders (CR

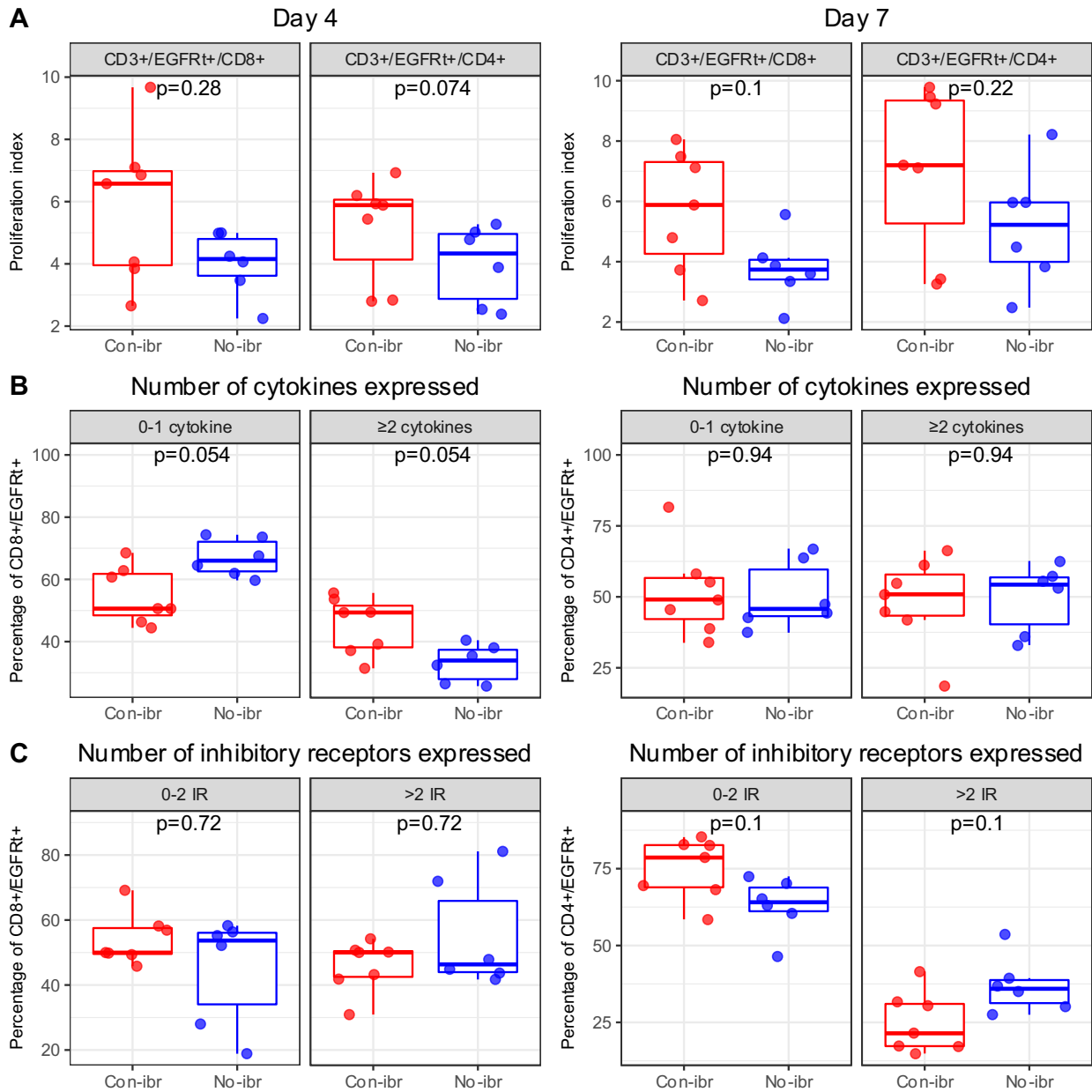
131 or PR) by 2018 iwCLL criteria (**C, D**). Broken lines show the 95% confidence intervals.

132 Abbreviations: Con-ibr, concurrent ibrutinib; No-ibr, ibrutinib discontinued prior to

133 lymphodepletion; CAR, chimeric antigen receptor. p values from logrank test.

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135 **Figure S6. Ibrutinib prior to leukapheresis and end-manufacturing CAR-T cell function**



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138 (A) End-manufacturing CAR-T cell products were stimulated with K562-parental or K562-CD19 cells at an
 139 effector:target ratio of 4:1 and analyzed at 4 and 7 days post-stimulation using flow cytometry. Gates were defined as
 140 singlets/viable/CD45⁺/CD3⁺/EGFR⁺/CD4⁺/ or singlets/viable/CD45⁺/CD3⁺/EGFR⁺/CD4⁺. The proliferation index is the
 141 ratio of the CFSE MFI of K562-parental-stimulated/K562-CD19-stimulated cells in the gated populations; (B)
 142 Intracellular cytokine staining by flow cytometry (IFN γ , TNF α , IL-2, CD107a) of end-manufacturing CAR-T cell products
 143 after stimulation at a 1:1 ratio with K562-parental or K562-CD19 cells for 24 hours and incubated with GolgiStopTM
 144 for the last 6 hours of stimulation. (C) Inhibitory receptor expression analysis by flow cytometry (PD-1, TIM-3, LAG-3, 2B4,
 145 CD160, KLRG1, TIGIT). Two-sided p values from Wilcoxon test. Bold horizontal lines, median; box, interquartile range
 146 (IQR); vertical lines, quartiles \pm 1.5xIQR. Data obtained from end-manufacturing CAR-T cells from 13 patients (Con-ibr,
 147 n= 6; No-ibr, n=7) Abbreviations: chimeric antigen receptor-engineered T (CAR-T); Ag, antigen; CFSE,
 148 carboxyfluorescein succinimidyl ester; Con-ibr, concurrent ibrutinib; No-ibr, no ibrutinib.

149 **Inclusion and exclusion criteria (NCT01865617)**

150 ***Inclusions for Screening and Leukapheresis***

- 151 1. Patients with CD19-expressing CLL, acute lymphoblastic leukemia, or non-Hodgkin
152 lymphoma
- 153 2. Male or female subject, greater than or equal to 18 years of age.
- 154 3. Ability to understand and provide informed consent.
- 155 4. Not HIV infected.

156 ***Inclusions for CAR-T cell Therapy for CLL***

- 157 1. Patients with CLL who are beyond first remission and who have failed combination
158 chemoimmunotherapy with regimens containing a purine analogue and anti-CD20
159 antibody or who were not eligible for such therapy. Patients with CLL for whom ibrutinib
160 is now standard first line therapy, must have progressed on ibrutinib. Patients with
161 fludarabine refractory disease are eligible. Patients may be treated following allogeneic
162 HCT. For the concurrent ibrutinib cohort, patients must agree to continue on or be
163 restarted on ibrutinib and must not have had prior intolerance to ibrutinib that would
164 prevent this. Patients managed with prior dose reductions for toxicity will continue at the
165 reduced dose for the remainder of this study.
- 166 2. Confirmation of diagnosis
- 167 3. Evidence of CD19 expression by immunohistochemistry or flow cytometry on any
168 prior or current tumor specimen or high likelihood of CD19 expression based on
169 disease histology.
- 170 4. Karnofsky performance status > 60%
- 171 5. All patients of childbearing potential must be willing to use a contraceptive method

172 before, during, and for at least two months after the T cell infusion.

173 6. Ability to understand and provide informed consent.

174 ***Exclusions for CAR-T cell Therapy for CLL***

175 1 . Patients requiring ongoing daily corticosteroid therapy at a dose of > 15 mg of
176 prednisone per day (or equivalent). Pulsed corticosteroid use for disease control is
177 acceptable.

178 2. Active autoimmune disease requiring immunosuppressive therapy is excluded unless
179 discussed with the PI.

180 3. Major organ dysfunction defined as:

181 a. Serum creatinine > 2.5 mg/dL

182 b. Significant hepatic dysfunction (SGOT > 5x upper limit of normal; bilirubin > 3.0
183 mg/dL)

184 c. Patients with clinically significant pulmonary dysfunction, as determined by
185 medical history and physical exam should undergo pulmonary function
186 testing. Those with an FEV1 of < 50% of predicted or DLco (corrected) < 40% will
187 be excluded.

188 d. Significant cardiovascular abnormalities as defined by any one of the following:
189 NYHA class III or IV congestive heart failure, clinically significant hypotension,
190 uncontrolled symptomatic coronary artery disease, or a documented ejection fraction
191 of <35 years old.

192 4. Uncontrolled active infection.