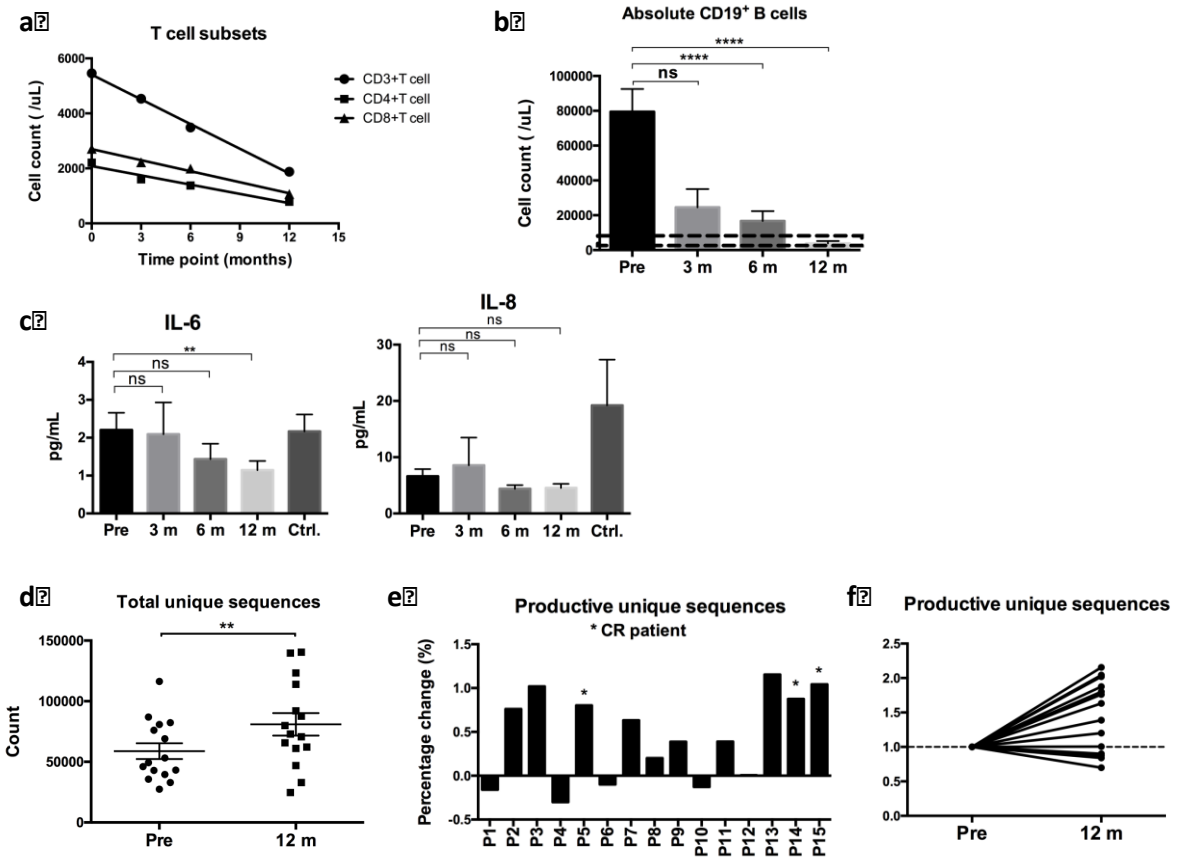
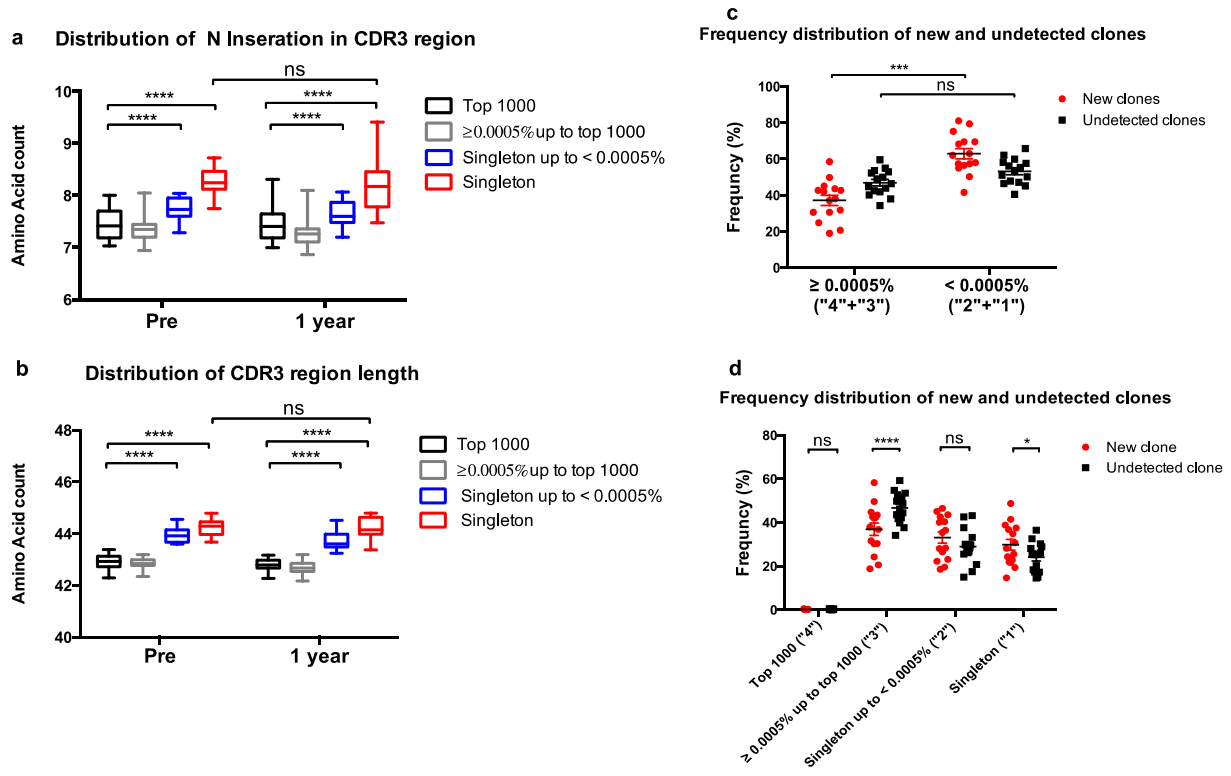
Supplemental Table 1. Clinical characteristics of entire cohort of CLL patients included in the study (n = 29)

Characteristic	Category	N (frequency, %) or median (range)
Sex	Female	12 (41.4)
	Male	17 (58.6)
Age (years)		65 (48 - 75)
Time (from diagnosis to ibrutinib therapy), years		8.5 (0 - 15)
Rai stage	0	0 (0.0)
	I	7 (24.1)
	II	3 (10.3)
	III	4 (13.8)
	IV	15 (51.7)
Cytogenetic abnormalies (FISH)	Del 17p	14 (48.3)
	Del 11q	8 (27.6)
	Trisomy 12	2 (6.9)
	Diploid	1 (3.4)
	Del 13q	4 (13.8)
Survival status	Alive	27 (93.1)
	Dead	2 (6.9)
IgVH	Mutated	1 (3.4)
	Unmutated	24 (82.8)
	Unknown	4 (13.8)
CD38	Positive	13 (44.8)
	Negative	16 (55.2)
ZAP-70	Positive	18 (62.1)
	Negative	9 (31.0)
	Unknown	2 (6.9)
Disease status	CR	7 (24.1)
	PR	22 (75.9)
Prior treatment	Chemo-immunotherapy	22 (75.9)
	No treatment	7 (24.1)

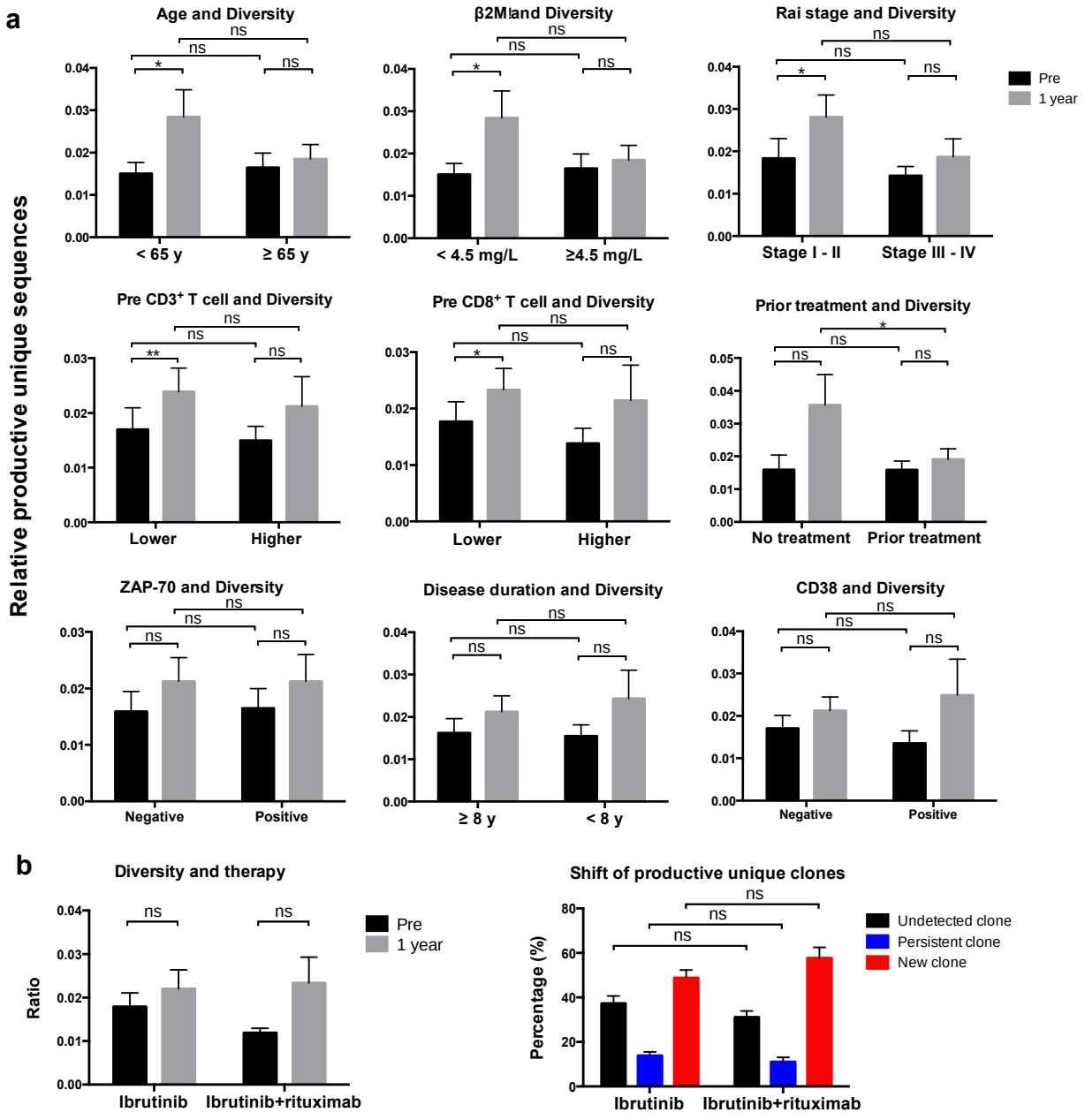
CR, complete remission; PR, partial remission.



Supplemental Figure 1. T cell subset and CD19$^+$ B cell counts decreased and TCRβ repertoire diversity improved over time during ibrutinib therapy. (**a**) There were negative correlations between the decline of CD3$^+$, CD4$^+$, and CD8$^+$ T cell counts and the time on ibrutinib or ibrutinib/rituximab therapy, (CD3$^+$ T cells: r = -0.998, P = 0.0016; CD4$^+$ T cells: r = -0.980, P = 0.0199; and CD8$^+$ T cells: r = -0.995, P = 0.0055) and CD4$^+$ and CD8$^+$ T cell counts synchronously declined (r = 0.9811, P = 0.0189) during ibrutinib therapy, accompanied by the decline of CD19$^+$ B cell counts (**b**). The bars in panel B represent mean values, and dotted lines indicate the normal range. **(c)** Plasma levels of IL-6 and IL-8 at the indicated time points, Ctrl correspond to control group. (**d**) The total number of unique sequences significantly increased after ibrutinib therapy. (**e**) An increase in productive unique sequences ("richness" of the clones) was found in 11 of 15 patients. Asterisks showed patients P5, P14, and P15 had complete remissions (CR) at 1 year. (**f**) Pretreatment values were normalized to 1 to show increases and decreases after treatment in a comparable manner. "Pre", "3 m", "6 m", and "12 m" refer to pretreatment, 3 months, 6 months, and 12 months after ibrutinib therapy, respectively. (Asterisks represent statistical significance; ** P < 0.01, **** P < 0.0001; ns, not significant.)



Supplemental Figure 2. N-insertion amino acid counts and TCRβ CDR3 region length in the clones with different frequencies and proportional analyses of new and undetected clones with different clonal frequencies after ibrutinib therapy. All unique clones from each sample were seemed as a whole, then, ranked in 4 groups according to their frequencies, from "singleton" clones (group "1") to the top 1000 clones (group "4"). (**a**) Both N-insertion amino acid counts in the CDR3 region and (**b**) TCRβ CDR3 region length were significantly higher in low-frequency clones than those in high-frequency clones. "Pre" refers to pretreatment. (**c**) A median 61.95% of new clones belonged to relatively small clones with less than 0.0005% frequency (groups "2" + "1"). (**d**) A median 31.14% of clones were undetected 1 year after ibrutinib therapy, mainly derived from the clones with relatively high frequency (greater than 0.0005% frequency, groups "3"). (* $P < 0.05$, ***$P < 0.005$, **** $P < 0.0001$; ns, not significant.)



Supplemental Figure 3. Association between TCRβ repertoire diversity and clinical characteristics and different treatment regimens. (**a**) No impact on TCRβ repertoire diversity recovery after 1 year of ibrutinib therapy was seen for ZAP-70 status, CD38 status, or disease duration. However, patients who had no prior treatment had broader TCR repertoire diversification than the patients had prior treatments at 1 year of ibrutinib. Factors significantly associated with higher TCR diversity 1 year after ibrutinib therapy were age (< 65 years), low β2M level (< 4.5 mg/L), low Rai stage, low pretreatment $CD3^+$ and $CD8^+$ ALCs. (**b**) TCRβ repertoire diversity did not significantly differ between CLL patients treated with ibrutinib or ibrutinib plus rituximab. "Pre" refers to pretreatment. (ns, not significant.) "Pre" refers to pretreatment. (* $P < 0.05$, ** $P < 0.01$; ns, not significant.)