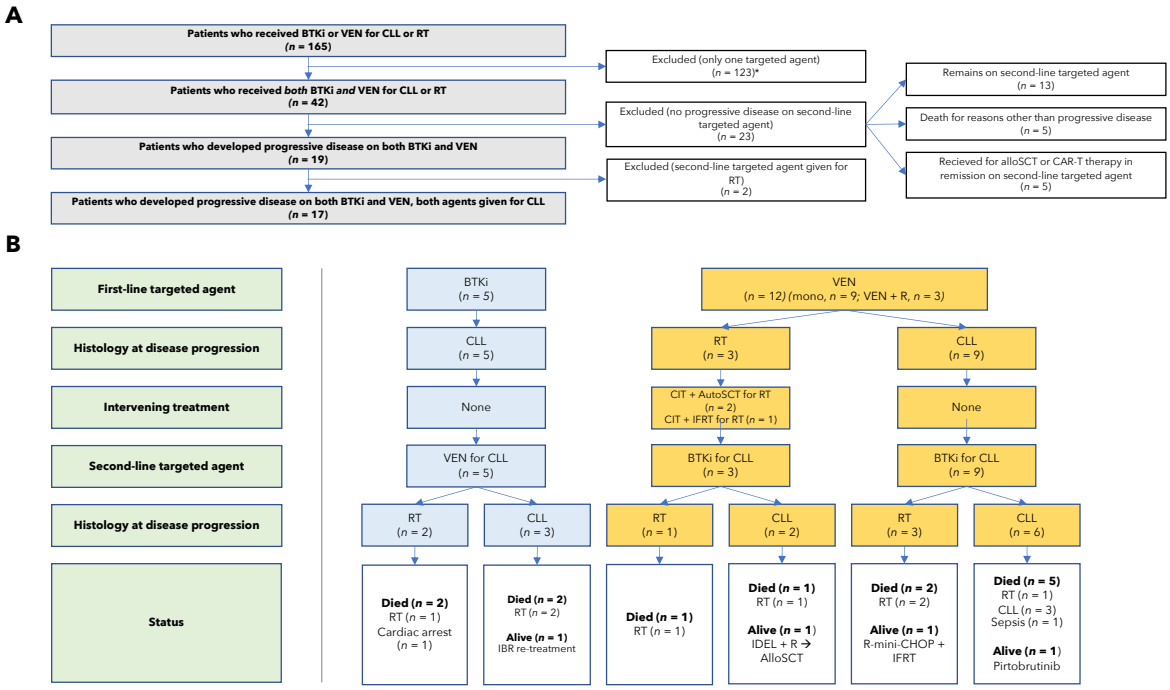
Supplementary material

Supplementary Table 1. Univariate analysis of clinico-pathological variables for association with overall survival after development of progressive disease after second-line targeted agent

Characteristic	*n* =		HR	logrank *p*-value
Age ≥ 76 years	Y	10	2.4 (0.63 - 9.26)	0.184
	N	7		
VEN as first TA	Y	12	1.211 (0.36 - 4.06)	0.756
	N	5		
Prior RT	Y	3	0.25 (0.03 - 2.00)	0.161
	N	14		
Total duration of disease control with VEN - BTKi ≥ median (54 months)	Y	8	2.30 (0.64 - 8.21)	0.188
	N	9		
F-refractory	Y	9	2.7 (0.68 - 10.86)	0.145
	N	8		
≥ 4 lines of prior therapy before second TA	Y	13	1.1 (0.28 - 4.29)	0.894
	N	4		
del(17p) and/or *TP53* mutation	Y	15	1.00 (0.20 - 4.97)	0.997
	N	2		
Richter transformation on second TA	Y	6	1.8 (0.52 - 6.42)	0.341
	N	11		

Supplementary Figure 1. Inclusion and exclusion process to select a cohort of patients with CLL resistant to BTKis and venetoclax



A. Inclusion and exclusion process for study cohort. Gray shading indicates patients whose records were reviewed. White shading indicates patients who were excluded and provides the reason.
B. Treatment sequence and features of progressive disease for study cohort. Yellow shading indicates patients who received venetoclax as their first targeted agent. Blue shading indicates patients who received a BTKi as their first targeted agent. Green shaded boxes on the left specify the clinical and treatment events described to the right. White shaded boxes indicate patient status at last follow-up.

BTKi = Bruton tyrosine kinase inhibitor; VEN = venetoclax; VEN + R = venetoclax + rituximab; mono = monotherapy; CIT = chemo-immunotherapy; IFRT = involved field radiotherapy; RT = Richter transformation; CLL = chronic lymphocytic leukemia; AutoSCT = autologous stem cell transplantation; AlloSCT = allogeneic stem cell transplantation; IDEL + R = idelalisib and rituximab; CAR T = chimeric antigen receptor T-cell

*Two patients were excluded due to exposure to second-line targeted agent exposure for <30 days (death from cryptococcal infection within days of venetoclax initiation, *n*=1; lost to follow-up after 3 doses of ibrutinib due to transfer to external centre, *n*=1)