Supplementary Table 1. Clinicopathological characteristics of patients

	Age	Gender	Dx	RT	Last f/u	Rai	ZAP70	Karyotype*	FISH*
CLL011	44	F	1999	8/2015	10/2015[#]	1	+	normal	TP53 del
CLL012	54	F	2007	2/2014	04/2015[#]	0	+	complex	TP53 del
CLL015	49	F	2000		09/2012[#]		+	N/A	TP53 del Trisomy 12
CLL017	68	M	2012	3/2015	06/2015[#]	4	+	complex	TP53 del
CLL019	61	F	1988	6/2015	10/2015[#]	3	+	single loss	TP53 del
CLL020	46	M	2008	5/2015	06/2015[#]	4	N/A	complex	TP53 del
CLL021	66	M	2006		03/2016	0	N/A	complex	TP53 del Trisomy 12
CLL022	73	M	2008	6/2012 10/2015	02/2016[#]	1	+	normal	TP53 del Trisomy 12
CLL024	52	F	2007		03/2016	2	+	normal	del(13q)

*Latest pre-ibr time point. [#]patient deceased. N/A, data not available. Del, deletion.

Supplemental Table 2. Sample collection detail

Patient	Time point	Abbreviation used	Sample Type	Days between consecutive time points
CLL011	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		8
	Responding1	Resp1	BM	343
	Responding2	Resp2	BM	180
	Relapse	Rel	BM	80
	RT	RT	FFPE (lymph node)	134
CLL012	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		2375
	Relapse	Rel	PB	315
	RT	RT	FFPE (pleural effusion)	20
CLL017	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		609
	RT	RT	FFPE (lymph node)	59
	Relapse1	Rel1**	BM	10
	Relapse2	Rel2**	PB	81
CLL019	Pre Ibr1	Pre-Ibr1	FFPE (nasal)	
	Pre Ibr2	Pre-Ibr2	BM	722
	Ibr initiation	Ibr init		14
	RT	RT	FFPE (liver)	763
	Relapse1	Rel1	PB	8
	Relapse2	Rel2	PB	84
CLL020	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		21
	RT*	RT	FFPE (lymph node)	91
	Relapse	Rel	PB	20
CLL022	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		136
	RT*	RT	FFPE (lymph node)	593
	Relapse	Rel	PB	15
CLL015	Pre Ibr	Pre-Ibr	PB	
	Ibr initiation	Ibr init		55
	Responding	Resp	PB	109
	Relapse1	Rel1	PB	487
	Relapse2	Rel2	PB	27
CLL021	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		17
	Relapse	Rel	PB	861
CLL024	Pre Ibr	Pre-Ibr	BM	
	Ibr initiation	Ibr init		8
	Relapse	Rel	BM	820

*This lymph node has both RT and CLL components, which were macro-dissected and analyzed separately

**Rel1 and Rel2 are sample codes and do not represent two different clinical relapses for the patients.

Supplementary Table 3. CNA and gene mutation detail in pre vs rel sample for each patient.

	Pre sample		Rel sample		Pre-specific		Rel-specific	
	CNA	Gene mutation	CNA	Gene mutation	CNA	Gene mutation	CNA	Gene mutation
CLL011	10	28	12	27	0	4	2	3
CLL012	7	21	22	24	0	2	15	5
CLL017	3	32	3	33	0	0	0	1
CLL019	5	24	5	24	0	0	0	0
CLL020	5	19	7	20	0	0	2	1
CLL022	2	21	4	25	1	2	3	6
CLL015	11	26	10	26	1	2	0	2
CLL021	7	27	7	27	0	0	0	0
CLL024	4	15	3	17	1	0	0	2

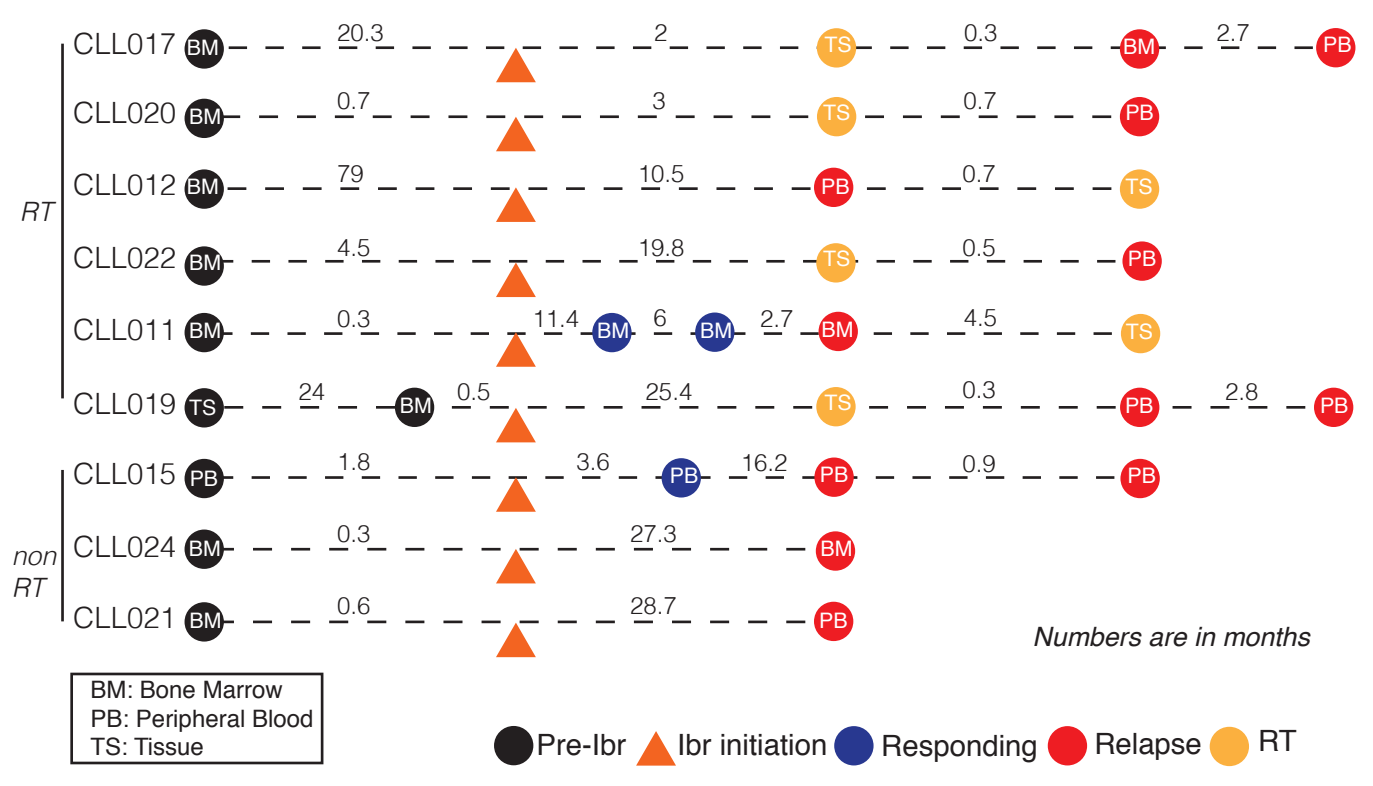
*This table supplements Figure 3 and the pre and rel samples compared are denoted in Fig 3A.

Supplementary Table 4. Confirmation of minor BTK mutant clones by high-depth sequencing

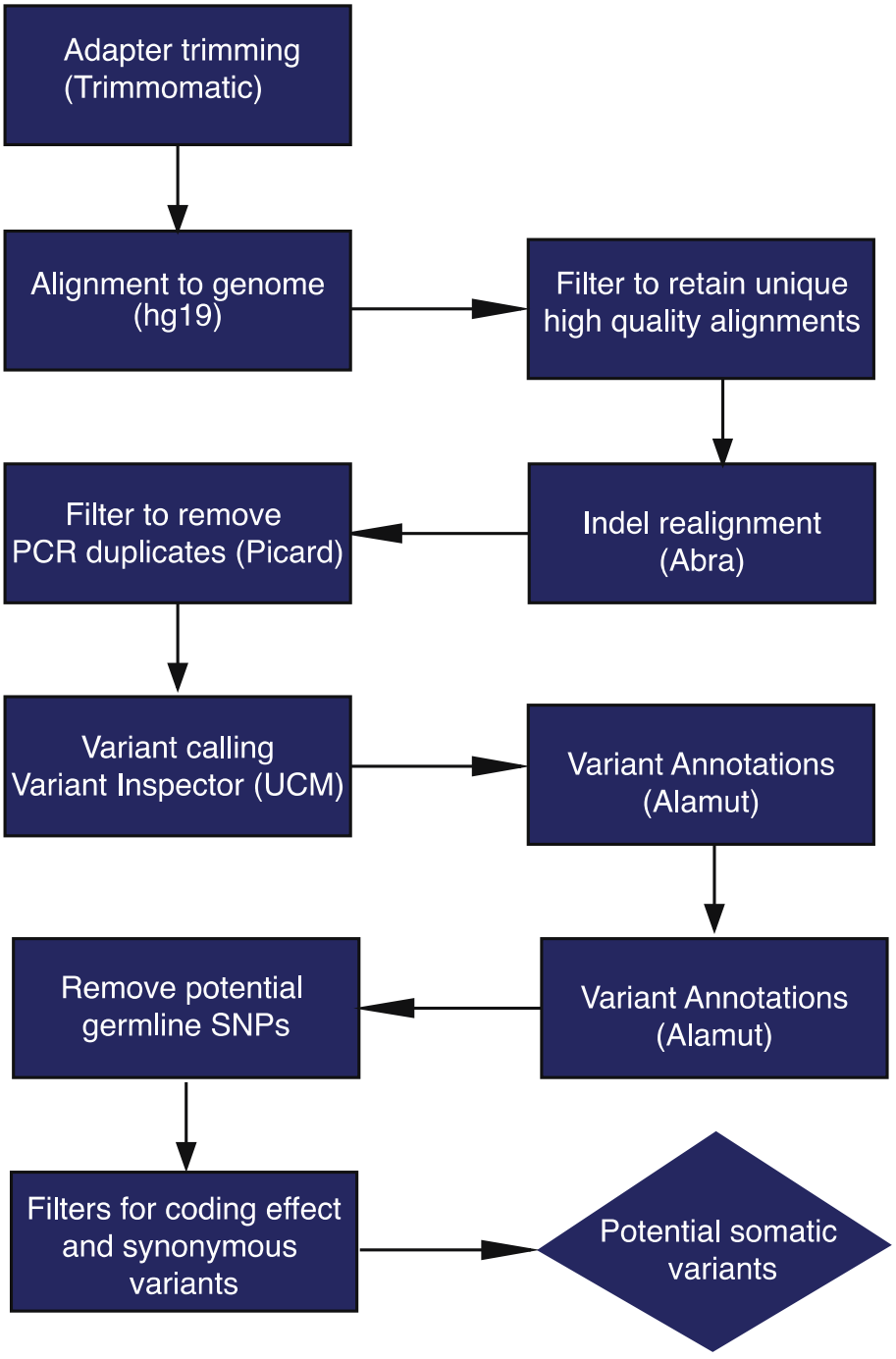
Patient	Sample*	Variant	Position	Ref	Alt	OncoPlus		CLL panel		Repeat CLL panel	
						$Depth_{Q30}$	MAF(%)	$Depth_{Q30}$	MAF(%)	$Depth_{Q30}$	MAF(%)
CLL012	Rel	C481S	100611164	C	G	228	2.6	497	3.6	7052	3.8
		C481R	100611165	A	G	225	1.3	494	1.4	7049	1.6
CLL019	Rel1	C481S	100611164	C	G	865	5.2	9517	6.7		
CLL015	Rel1	C481R	100611165	A	G	446	3.8				
		C481S	100611164	C	G	445	1.1				
	Rel2	C481R	100611165	A	G	525	2.9				
		C481S	100611164	C	G	528	1.9				
	Rel3[#]	C481R	100611165	A	G			14323	2.2	1247	3.8
		C481S	100611164	C	G			14334	0.5	1248	0.7

*See Suppl. Table 2 for sample detail

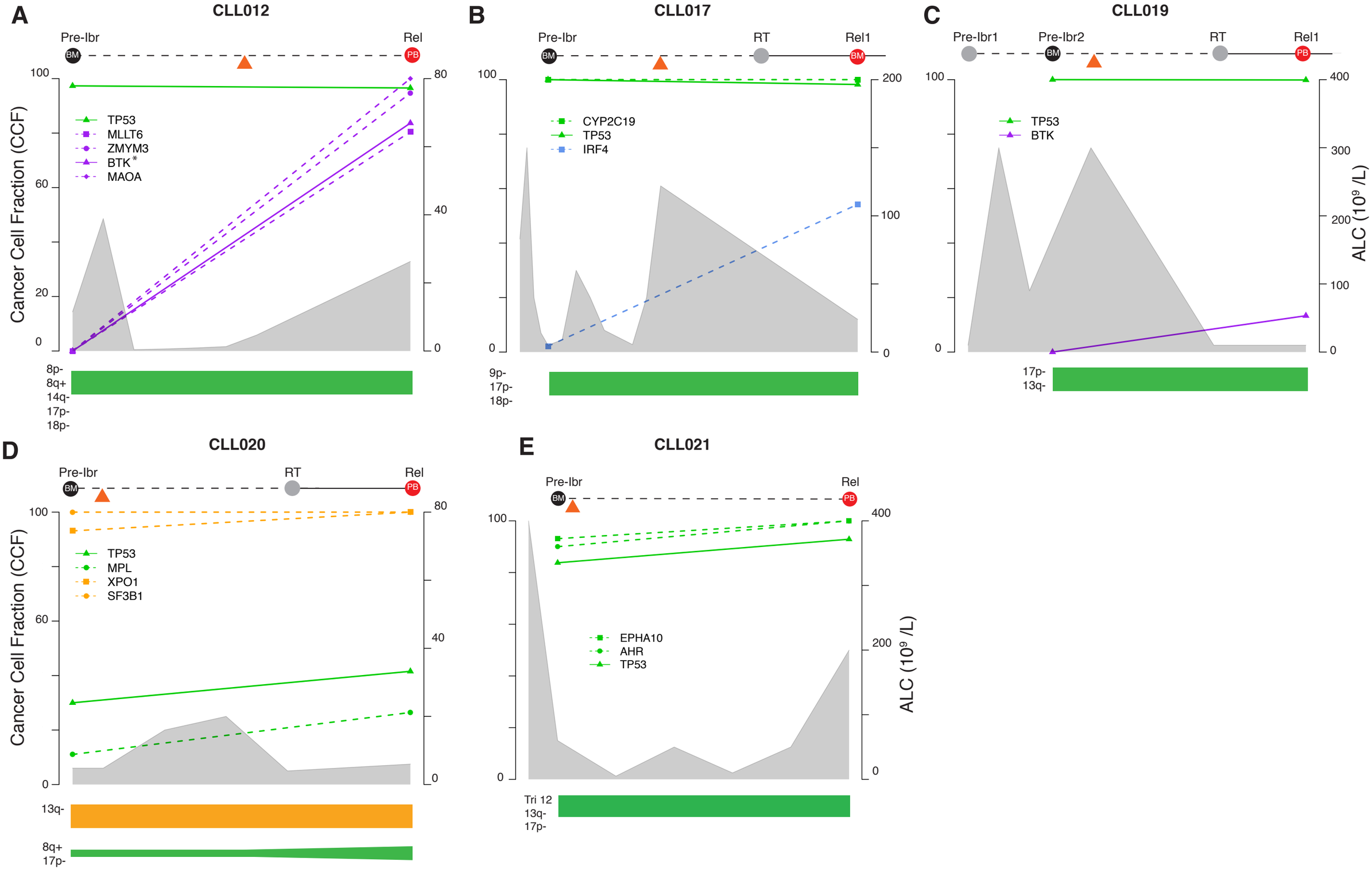
[#]In CLL015, the sample Rel3 was taken 2 months after sample Rel2 while the patient was still on ibr. It was used to confirm the existence of minor clones because samples Rel1 and Rel2 were exhausted.


RT
non RT
CLL017 BM 20.3 2 TS 0.3 BM 2.7 PB
CLL020 BM 0.7 3 TS 0.7 PB
CLL012 BM 79 10.5 PB 0.7 TS
CLL022 BM 4.5 19.8 TS 0.5 PB
CLL011 BM 0.3 11.4 BM 6 BM 2.7 BM 4.5 TS
CLL019 TS 24 BM 0.5 25.4 TS 0.3 PB 2.8 PB
CLL015 PB 1.8 3.6 PB 16.2 PB 0.9 PB
CLL024 BM 0.3 27.3 BM
CLL021 BM 0.6 28.7 PB
Numbers are in months
BM: Bone Marrow
PB: Peripheral Blood
TS: Tissue
Pre-Ibr
Ibr initiation
Responding
Relapse
RT

Supplemental Figure 2



Supplementary Figure 3



Suppl Figure legends

Suppl. Fig. 1. Schematic diagram of patient sample collection sorted by duration of response. The line diagrams summarize sample collection for each of the 9 patients (6 with RT and 3 non-RT), with reference to ibr-initiation (orange triangle). In each group, the patients are sorted in increasing order of duration of response (DOR). The samples to the left of ibr initiation represent the Pre-Ibr time points. The lines are not drawn to scale. Types of sample are noted (BM: Bone marrow, PB: Peripheral Blood, TS: Tissue).

Suppl. Fig. 2. Custom-designed bioinformatics pipeline for detection of somatic variants from UCM-OncoPlus data. The adapter-trimmed reads are aligned to the hg19 genome, filtered to remove low quality alignments and indel-realigned. PCR duplicates are then removed and variant calling is performed using a UCM variant caller, Variant Inspector. All resulting variants are annotated using Alamut, after which all potential germline SNPs and synonymous non-exonic variants are removed to generate a list of potential somatic variants.

Suppl. Fig. 3. Evolutionary dynamics of the major clones during ibr relapse. Clonal trends in additional patients patients). **A-E)** Detailed trends for CLL012, 017, 019, 020 and 021. Samples being analyzed are shown on the top of the plots. Time on the X-axis is partially scaled consistent with Fig. 1. Clonal frequencies are shown on the left Y-axis while ALC values are shown on the right Y-axis (grey shaded curves). Mutations that clustered in the same trends are shown in the same colors (Green: TP53

clusters, Purple: BTK clusters, and Yellow: SF3B1 clusters). The clonal trends of the copy number changes are shown below each plot using the same color scheme.