Probe target	Chromosome location	Manufacturer
TP53	17p13.1	Abbott Molecular
ATM	11q22.3	Abbott Molecular
D12Z3	12 centromere	Abbott Molecular
D13S319 (LAMP control)	13q14.3	Abbott Molecular
BCL6 (break-apart)	3q27	Abbott Molecular
CMYC (break-apart)	8q24	Abbott Molecular or Poseidon
SEC63 and/or MYB	6q21/6q23	Kreatech or Poseidon
REL (DIRC1 control)	2p16/2q32.1	Empire Genomics
IGH/CCND1	14q32.3/11q13.3	Abbott Molecular

Table S1: FISH probes. Hybridizations were performed according to the manufacturer's directions. All patients included in the study received this panel testing, with the exception of the CCND1/IGH probes if the patient had this test performed on a previous sample and REL/DIRC1 if there was insufficient sample.

Patient	Classification for Discontinuation	FISH nomenclature
1	CLL	nuc ish(RELx3~7,DIRCx3~6)[72/200],(BCL6x4)[58/247]/(BCL6x3)[11/247],(SEC63x1)[158/206],(MYCx4)[129/245]/(MYCx3)[57/245],(ATMx2,TP53x1)[162/219]/(ATMx4,TP53x3)[45/219],(D12Z3x3,D13S319x2)[62/237]/(D12Z3x4,D13S319x2)[62/327]/(D12Z3x2,D13S319x1)[52/237]
2	Richter's	nuc ish(RELx6,DIRC1x4)[48/200]/(REL,DIRC1)x4[47/200],(BCL6x4)[110/200],(MYBx4,ATMx4,TP53x2)[110/200]/(MYBx2,ATMx2,TP53x1)[83/200],(MYCx4)[120/200],(CCND1x4,IGHx3)[120/200],(D12Z3,D13S319)x4[111/200]
3	Richter's	nuc ish(BCL6x4)[16/217],(SEC63x2,MYCx3)[13/218]/(SEC63x2,MYCx4)[18/218],(ATMx1,TP53x2)[46/221]/(ATMx4,TP53x2)[12/221]/(ATMx4,TP53x3)[7/221],(D12Z3x2,D13S319x1)[41/235]/(D12Z3,D13S319)x4[25/235]
4	Richter's	nuc ish(BCL6x3)[84/231]/(BCL6x4)[52/231],(SEC63x4)[143/203],(MYCx4)[90/264]/(MYCx5)[41/264]/(5'MYCx6,3'MYCx4)(5'MYC con 3'MYCx4)[18/264],(ATMx4,TP53x2)[112/216],(D12Z3x4,D13S319x3,LAMPx3)[90/259]/(D12Z3x5,D13S319x3,LAMPx3)[47/259]/(D12Z3x3,D13S319x2,LAMPx2)[14/259]
5	Richter's	nuc ish(REL,DIRC1)x4[74/200],(BCL6x4)(5'BCL6 sep 3'BCL6x2) [12/238]/(5'BCL6x4,3'BCL6x5)(5'BCL6 con 3'BCL6x2)[10/238]/ (5'BCL6x3, 3'BCL6x5)(5' BCL6 con 3'BCL6x2)[10/238]/(BCL6x2) (5'BCL6 sep 3'BCL6x1)[3/238],(SEC63,MYC)x4[31/231],(CCND1,IGH)x4[26/226],(ATM,TP53)x4[28/229],(D12Z3,D13S319)x4[29/229]
6	Richter's	nuc ish(BCL6x4)[17/217],(SEC63x4)[12/222],(MYCx6)[29/239]/(MYCx3) [6/239]/(MYCx4)[4/239],(CCND1,IGH)x4[12/212],(ATMx4,TP53x2)[11/225]/(ATMx2,TP53x1)[184/225],(D12Z3x3,D13S319x4,LAMPx4)[19/221]/(D12Z3,D13S319,LAMP)x4[4/221]
7	Richter's	nuc ish(BCL6x4)[28/228],(SEC63x3)[32/244],(MYCx3)[162/272]/(MYCx6)[54/272],(CCND1x2,IGHx3)[128/234]/(CCND1x4,IGHx6)[42/234],(ATMx2,TP53x1)[170/250]/(ATMx4,TP53x2)[37/250],(D12Z3,D13S319)x4[37/237]

8	-	nuc ish(BCL6x4)[152/227],(SEC63,MYC)x4[151/226]/(SEC63,MYC)x3[20/226]/(SEC63x3,MYCx4)[9/226]/(SEC63x2,MYCx3)[8/226]/(SEC63x2,MYCx4)[8/226],(MYBx3,ATMx2,TP53x2)[191/377]/(MYBx4,ATMx2,TP53x2)[98/377],(MYBx2,ATMx1,TP53x1)[41/377],(D12Z3,D13S319)x4[209/331]/(D12Z3x4,D13S319x2)[29/331],(D12Z3,D13S319)x3[10/331]/(D12Z3x3,D13S319x4)[22/331],(3'IGHx3,5'IGHx2)(3'IGH con 5'IGHx1) (3'IGH con 5'IGH dimx1)[155/215]/(3'IGHx4,5'IGHx2) (3'IGH con 5'IGHx1)(3'IGH con 5'IGH dimx1)[18/215]
9	-	nuc ish(BCL6x4)[25/225],(SEC63,MYC)x4[32/232],(ATMx2,TP53x1)[142/226]/(ATMx4,TP53x2)[29/226],(D12Z3x4,D13S319x3,LAMPx3)[21/228]/(D12Z3,D13S319,LAMP)x4[7/228]

Table S2. FISH results for patients with near-tetraploidy in CLL.

Patient	Classification for Discontinuation	Karyotype
1	CLL	44,XY,del(9)(p22),psu dic(17;6)(p13;q21),dic(18;20)(p11.2;p11.2)[cp12]/45,sl,add(X)(q28),+add(9)(p22),-del(9)(p22),dic(15;21)(p11.2;p11.2),+18,-dic(18;20),+20,+mar1[2]/**90-91,sdl1x2,+add(X),+add(X),-Y,+add(9)(q22)x4,-add(9)(p22),-add(9)(p22),+mar2[2]**/44,sl,del(13)(q12q21.2)[5]
2	Richter's	**44,XY,psu dic(7;3)(3qter>3q21::?::3q21>3p21::?::7p15>7qter),add(9)(q34),-17,add(21)(p11.2)[cp11,one is 4n]**/43,sl,inv(12)(p13q24.1),dic(14;18)(p11.1;p11.1)[cp15]/46,XY[1]
3	Richter's	**44-45,X,-Y,-2,+del(3)(p21),-6,-9,add(11)(q13),del(11)(q21),-17,-21,+mar1,+mar2,+mar3[cp6,one is 4n]/82-86<4n>,XXYY,+X,-1,add(3)(q27)x2,-6,-6,der(?;9)(?;q10)x2,-14,-14,-15,-15,-16,add(21)(q22)x2,+mar4,+mar5 [cp3]**/46,XY[7]/nonclonal[4]
4	Richter's	**77-82<4n>,XX,-Y,-Y,-1,-3,add(3)(p25),-8,add(8)(p11.2)[4],-9,-9,-10,-12,del(12)(p12),-13,-14,add(14)(p13)[3],-15,-15,i(17)(q10)x2,-18[4],-20,+21[5],add(21)(p13),-22[8],add(22)(p13),+mar1,+mar2,+mar3,+mar4,+mar5[cp11]**/46,XY[9]
5	Richter's	**89-90<4n>,XXYY,der(1)del(1)(p13p31)del(1)(q32q42),-4,-5,-8,-9,-18,+mar1,+mar2[cp2]/93-112<4n>,XXYY,+add(1)(q13)[cp2]**/46,XY[12]/nonclonal[4]
6	Richter's	43-44,X,-Y,der(2)t(2;11)(q13;q13),der(11)del(11)(p11.2p13)t(2;11)(q13;q13),-14,-15,der(17)t(15;17)(q13;p11.2),+der(?)t(?;Y)(?;q11.2)[cp13]/**82-87,slx2,+Y,+Y,add(1)(q42)x2,add(4)(p16)x2,-12,-der(?)t(?;Y),-der(?)t(?;Y)[cp4]**/44,sl,+8[2]/ nonclonal[1]
7	Richter's	46,XX,t(14;19)(q32.3;q13.2),der(17)t(8;17)(q13;p11.2),del(20)(q11.2)[cp15]/**91,slx2,-6[cp3]/91,sdl1,+der(17)t(8;17),-19[cp2]**
8	-	45,XX,del(11)(q13q23),dic(13;18)(p11.2;p11.2),i(17)(q10)[2]/45,sl,+add(11)(q13),-del(11)[3]/**88-89,sdl1x2,-14[cp2]/87,slx2,add(3)(p21),-14,-15[cp4]/85-88,slx2,-6,-14[cp8]**/46,XX[2]
9	-	**45,XX,der(4)t(4;17)(p16;q21),-17[cp6,one is 4n]**/45,sl,del(3)(p21),der(12)t(12;14)(q24.1;q24),der(14)t(3;14)(q21;q11.2)[cp5]/**86-88,slx2,-3,der(14)t(3;14)(p21;q22)ins(14;?)(q22;?),-15[cp5]**/45,sl,add(X)(p22.1),t(1;5) (p13;q13),t(3;11)(q29;q21),add(10)(q24),add(21)(q22.3)[3]

Table S3: Complete karyotypes of near-tetraploid patients. Near-tetraploidy clones are in bold.

Patient	Classification for Discontinuation	REL	BCL6	SEC63 or MYB	MYC	ATM/ TP53	D12Z3/ D13S319	CCND1/ IGH
1	CLL	36.0%	23.5%	23.3%	52.7%	20.5%	19%	ND
2	Richter's	47.5%	55.0%	55.0%	60.0%	55.0%	55.5%	60%
3	Richter's	9.5%	7.4%	8.3%	8.3%	8.6%	10.6%	ND
4	Richter's	37.0%	58.8%	70.4%	56.4%	51.9%	52.9%	ND
5	Richter's	19.0%	13.4%	13.4%	13.4%	12.2%	12.6%	11.50%
6	Richter's	12.0%	7.8%	5.4%	13.8%	4.9%	10.4%	5.70%
7	Richter's	ND	12.3%	13.1%	19.9%	14.8%	15.6%	17.90%
8	-	78.0%	67.0%	74.3%	74.3%	76.7%	81.6%	80.50%
9	-	14.0%	11.1%	13.8%	13.8%	12.8%	12.3%	ND

Table S4: Percentage of cells for each probe set interpreted as having a near-tetraploid signal pattern in the near-tetraploid patients. A count was interpreted as being near-tetraploidy if one of the following conditions was met: there were 4 signals present for a probe, the count was a doubling of a diploid clone count, or the percentage of the count was consistent with the tetraploid clone size seen with other probes. Abbreviation: ND, not done

Outcome	Total (n = 297)	Not near-tetraploid (n = 288)	Near-tetraploid (n = 9)	P-value
Cuminc: CLL Progression				
Number of Events	52	51	1	
% at 1y (95% CI)	0.7 (0.1-2.3)	0.7 (0.1-2.4)	0	0.41
% at 2y (95% CI)	5.2 (3.0-8.1)	5.3 (3.1-8.4)	0	
% at 3y (95% CI)	11.1 (7.7-15.2)	11.1 (7.6-15.3)	11.1 (0.2-44.9)	
% at 4y (95% CI)	19.7 (14.7-25.3)	20.1 (14.9-25.8)	11.1 (0.2-44.9)	
Cuminc: Transformation				
Number of Events	28	22	6	
% at 1y (95% CI)	4.7 (2.7-7.6)	3.8 (2.0-6.5)	33.3 (6.7-64.0)	<0.0001
% at 2y (95% CI)	7.5 (4.9-10.9)	6.3 (3.9-9.6)	44.4 (11.7-73.6)	
% at 3y (95% CI)	9.4 (6.3-13.1)	7.6 (4.8-11.1)	66.7 (23.5-89.3)	
% at 4y (95% CI)	9.9 (6.7-13.7)	8.1 (5.2-11.7)	66.7 (23.5-89.3)	
Cuminc: Other Event				
Number of Events	72	72	0	
% at 1y (95% CI)	13.2 (9.6-17.3)	13.6 (9.9-17.8)	0	0.08
% at 2y (95% CI)	18.4 (14.2-23.0)	18.9 (14.6-23.7)	0	
% at 3y (95% CI)	23.7 (18.9-28.8)	24.5 (19.5-29.7)	0	
% at 4y (95% CI)	24.8 (19.9-30.1)	25.6 (20.5-31.1)	0	
Overall Survival				
Number of Events	86	81	5	
Median, years (95% CI)	NR	NR	2.5 (0.7-NR)	
% at 1y (95% CI)	87.2 (82.8-90.5)	87.5 (83.1-90.8)	77.8 (36.5-93.9)	0.08
% at 2y (95% CI)	80.4 (75.4-84.5)	80.8 (75.8-84.9)	66.7 (28.2-87.8)	
% at 3y (95% CI)	73.0 (67.5-77.8)	73.9 (68.3-78.7)	44.4 (13.6-71.9)	
% at 4y (95% CI)	69.0 (62.8-74.4)	69.8 (63.4-75.2)	44.4 (13.6-71.9)	

Table S5. In a cumulative incidence analysis, near-tetraploidy was significantly associated with transformation on ibrutinib. Associations were tested using Gray's test for cumulative incidence or the log-rank test for overall survival. Transformations include 1 peripheral T cell lymphoma, 1 composite B and T cell lymphoma, 1 plasmablastic lymphoma, 1 Hodgkin lymphoma, 1 prolymphocytoid progression, and 23 cases with diffuse large B cell lymphoma. All near-tetraploid transformations were diffuse large B cell lymphoma. Abbreviations: Tx, treatment, Cuminc, cumulative incidence, y, year(s)