Supplemental Table 1: Patients' characteristics

Patient #	Age	Gender	IgVH mutation	WBC 10^9/L	% lymphocytes	%CD19+/ CD5+ cells	FISH	Mutation	Treatment before sampling
1	73	M	M	ND	ND	13.3	13q-		none
2A	30	M	U	286	ND	65.4	11q-		FCR
2B	30	M	U	424.2	99	94.6	11q-		FCR
2C	27	M	U	160.5	94.6	93.8	11q-	ATM	none
3A	81	M	M	80.8	90.5	90.6	13q-		none
3B	80	M	M	86.4	87	93.4	13q-		none
4A	64	F	M	175	95.1	94	13q-		none
4B	62	F	M	62	87	90.7	13q-		none
5	77	F	M	120	94	93.3	ND		none
6	60	M	M	64.3	ND		13q-		none
7	42	M	M	66.6	92	86.3	13q-		none
8A	63	F	M	32.2	86.7	80.6	13q-		none
8B	66	F	M	23.8	80	88.8	13q-		none
9	74	F	M	102	86.7	99.8	none	NOTCH1	chlorambucil + prednisone
10	unknown	unknown	unknown	ND	ND	ND	none		unknown
11	unknown	unknown	unknown	ND	ND	ND	none		unknown
12	44	M	U	ND	ND	ND	11q-, 13q-	ATM	none
13	76	M	U	46.4	93.3	91.09	11q-, 13q-	ATM	chlorambucil
14	63	unknown	U	ND	ND	ND	11q-	ATM	none
15	70	unknown	U	ND	ND	ND	11q-	ATM	fludarabine + cyclophosphamide, fludarabine
16	74	M	U	127	ND	93	none		none
17	69	M	M	ND	ND	95.2	13q-		chlorambucil
18	62	M	U	192.1	92.9	94.9	13q-		none
19A	63	F	M	153.0	96.0	95.7	13q-, 17p-		chlorambucil, FCR

19B	62	F	M	173.0	ND	99.9	13q-	none
20	70	M	U	422	ND	92.8	17p-	chlorambucil, CVP/COP, FCR
21	56	F	M	ND	ND	94.7	13q-	none
22	67	F	M	88.7	ND	86.9	13q-	chlorambucil + prednison, fludarabine
23	62	F	M	84.8	ND	99.9	13q-	none
24	88	F	M	53.8	87.2	87.1	ND	none
25	83	F	M	56.8	87.6	88.1	13q-, tris12	none
26	61	F	M	46.1	ND	91.1	13q-	none
27	81	F	M	23.1	87.3	93.3	ND	none
28	44	F	M	115	ND	92.9	13q-	chlorambucil
29	46	M	M	12.8	72.4	99.5	ND	none
30	50	M	M	56.5	90	95.2	ND	none
31	86	M	M	90.5	90.8	81	13q-	chlorambucil
32A	56	M	U	78.1	ND	89.6	tris12	chlorambucil
32B	50	M	U	149	94	90	tris12	chlorambucil
33A	72	F	U	115.3	ND	90.3	tris12	none
33B	73	F	U	89.9	ND	91.4	tris12	none
33C	74	F	U	89.9	ND	91.4	tris12	none
34A	60	M	U	69.5	ND	94	13q-	none
34B	60	M	U	ND	ND	91	13q-	none
35A	73	M	U	116.8	ND	98.4	ND	none
35B	74	M	U	166.6	ND	84.2	ND	chlorambucil
36	60	M	U	21.9	75.1	99.2	ND	none
37	76	M	U	49.7	ND	88.6	13q-	none
38	52	M	U	132	92.1	86.2	tris12	none
39	65	M	M	ND	ND	92.1	none	none
40	60	F	U	265	ND	99.8	13q-	FCR
41	41	M	M	40	84	91.4	13q-	none
42	58	M	U	55.7	83	94.4	13q-	chlorambucil + fludarabine +

									cyclofosfamide
43A	55	F	U	272	ND	95.4	none		FCR
43B	55	F	U	180	ND	95.1	none		FCR
44	71	F	M	47.3	91.1	95.9	ND		none
45	60	M	M	85.5	94	95.8	13q-		none
46	65	F	U	89.9	90	89	ND		none
47	53	M	U	31.1	95.8	82.1	11q-	ATM	chlorambucil, radiotherapy, CVP/COP, FCR
48	44	M	U	ND	ND	ND	13q-, 11q-	ATM	none
49	68	unknown	U	ND	ND	ND	11q-	ATM	none
50	80	unknown	M	ND	ND	ND	11q-	ATM	none
51	70	unknown	U	ND	ND	ND	11q-	ATM	fludarabine + cyclophosphamide, fludarabine
52	77	unknown	U	ND	ND	ND	11q-	ATM	none
53	68	unknown	U	ND	ND	ND	11q-	ATM	none
54	44	unknown	U	ND	ND	ND	11q-	ATM	none
55	64	unknown	U	ND	ND	ND	11q-	ATM	fludarabine + cyclophosphamide, alemtuzumab
56	36	M	U	82.5	75.1	85.13	17p-	TP53	CVP/COP, FCR, alemtuzumab, R-CHOP, R-DHAP
57	59	M	U	ND	ND	ND	17p-	TP53	none
58	82	M	M	137	94.8	83.5	13q-, 17p-	TP53	chlorambucil, alemtuzumab
59	58	M	M	155	ND	87.9	tris12, 17p-	TP53	chlorambucil + prednison, R-CHOP, FCR, Rituximab, R-DHAP
60	63	unknown	U	ND	ND	ND	17p-	TP53	fludarabine + cyclophosphamide, R-CHOP, alemtuzumab
61	75	unknown	U	ND	ND	ND	17p-, 11q-	TP53	chlorambucil, FCR, alemtuzumab
62	67	F	U	ND	ND	99.6	none	SF3B1	chlorambucil, radiotherapy, CVP/COP, fludarabine
63	69	M	M	11.4	32.7	18.59	none	SF3B1	none

64	82	F	M	20.6	65.9	76.22	ND	SF3B1	chlorambucil
65	60	M	U	ND	ND	ND	11q-	SF3B1	none
66	72	M	unknown	87.9	86	82.4	13q-, 11q-	NOTCH1	chlorambucil, R-CVP, FCR + R-CHOP, dasatinib + fludarabine
67	76	M	M	31.9	96.1	91.74	none	NOTCH1	chlorambucil
68	73	M	M	47.3	86.8	89.29	none	NOTCH1	none
69	57	F	M	33.9	85.5	85.7	ND		none
70	76	M	M	74.1	76	99.1	ND		none
71	78	M	U	100	74	94.1	tris12		none
72	58	F	M	170.9	ND	97.9	13q-, tris12		chlorambucil, fludarabine + cyclophosphamide, fludarabine
73	63	F	M	92.7	ND	93.7	none		none
74	68	F	U	71.7	83.2	97	ND		none
75	78	M	U	100	74	94.1	tris12		none
76	75	F	M	92.9	91	85.9	ND		none
77	63	F	M	79.2	91,0	92.3	ND		none
78	80	M	M	149.4	92	98.2	none		chlorambucil
79	68	F	U	100.5	89	84.8	tris12		none
80	66	M	M	93.4	ND	90.8	none		none
81	73	M	U	108	94.7	96.4	17p-		chlorambucil, fludarabine, alemtuzumab, FCR
82	65	F	M	59	92	87.6	ND		none
83	50	F	M	80.2	96	91.4	ND		none
84	48	M	unknown	ND	ND	ND	13q-		R-CHOP
85	58	F	unknown	ND	ND	ND	11q-	ATM	none
86	76	F	unknown	ND	ND	ND	11q-, 13q-	ATM	none
87	72	M	unknown	ND	ND	ND	11q-	ATM	none
88	44	M	unknown	ND	ND	ND	11q-	ATM	none
89	63	M	unknown	ND	ND	ND	none		none
90	52	M	unknown	ND	ND	ND	none		none
91	75	F	unknown	ND	ND	ND	none		none

92	68	M	unknown	ND	ND	ND	none	none

Gender M: Male; F: Female, IgVH mutation M: Mutated; U: Unmutated, ND: not determined
A, B, C refer to different sampling times of the same patient;

FCR: fludarabine + cyclophosphamide + rituximab; CVP/COP: cyclophosphamide + vincristine/oncovin + prednisolone

R-CHOP: rituximab + cyclophosphamide + vincristine/oncovin + prednisolone; R-DHAP: rituximab + dexamethasone + cytarabine + cisplatin

Supplemental Table 2: Patient characteristics for clinical study CC-115-ST-001, CLL & SLL subjects

Patient #	Age	Gender	IgVH mutation	WBC 10^9/L	% lymphocytes	FISH	Mutation	Prior Treatment	Best Response
0011034*	62	F	unknown	4.8	27.0	11q-, 13q-	ATM	R-CHOP, FCR, R, BR, anti CD20 Ab	NE
2011004	54	M	unknown	100.7	90.7	11q-	ATM**	FC, alemtuzumab	PR
2011005	60	M	unknown	64.9	91.2	11q-	ATM	FCR	PD
2011007	50	F	U	65.3	89.5	11q-	ATM**	FCR	SD
3011019	75	F	unknown	17.4	89.4	11q-, 17p-	ATM**	CHOP, F, FCR, bendamustine, ofatumumab, R-CHOP, BR,	PR with lyphocytosis
4011001	57	M	U	32.2	61	11q-, 1q- DER 17;22	ATM	FC, BR, Dex alemtuzumab, lenalidomide	PR with lyphocytosis
4011002	54	M	unknown	65.8	64	11q-	ATM	FC, BR	PR with lyphocytosis
4011003	55	M	U	17.6	90	11q-	ATM	FCR, CHOP	NE

* SLL subject **Likely or potentially deleterious mutation in remaining ATM

U: Unmutated, NE: not evaluable, PR: partial response, PD: progressive disease, SD: stable disease

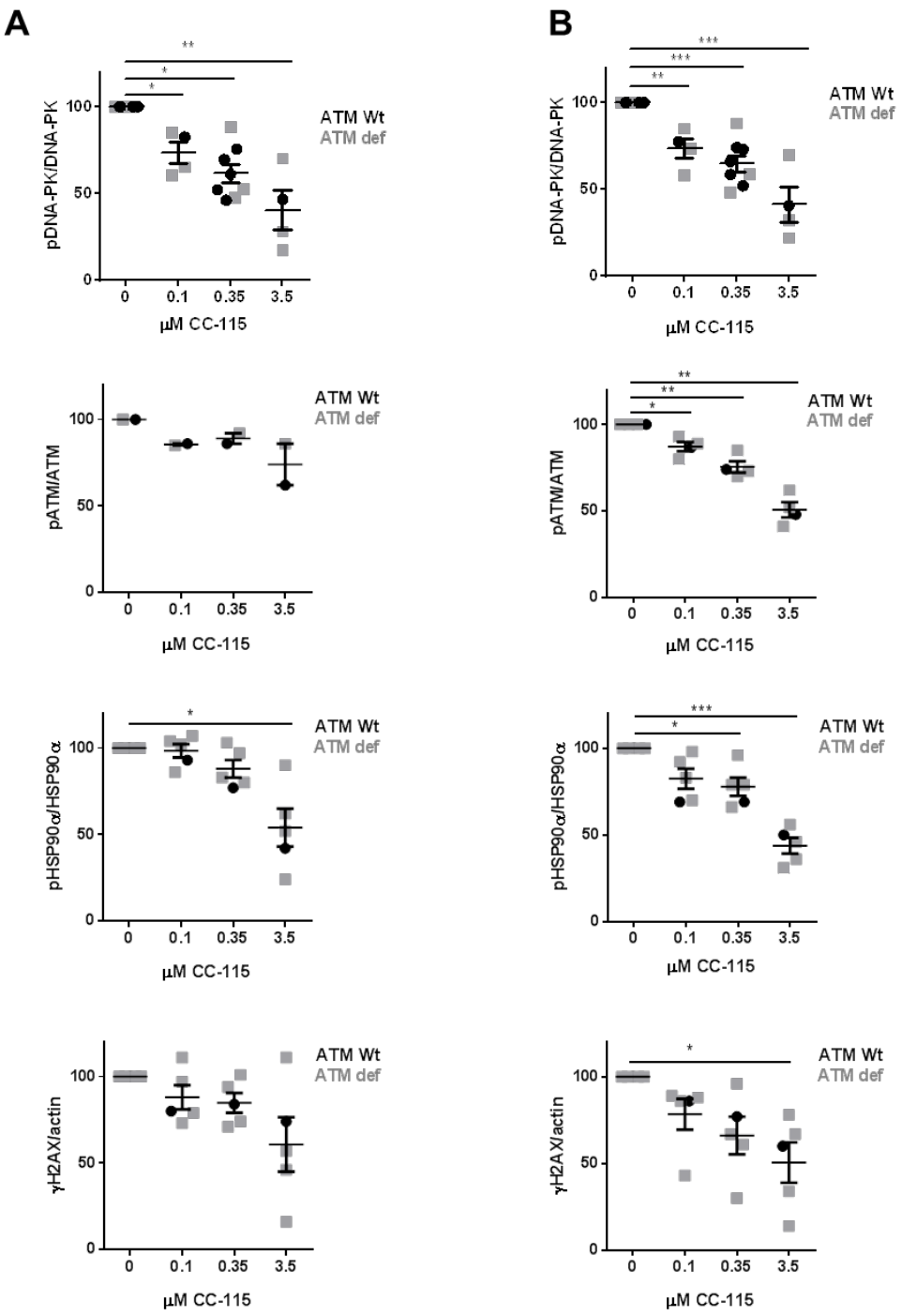
FCR: fludarabine + cyclophosphamide + rituximab; CVP/COP: cyclophosphamide + vincristine/oncovin + prednisolone; Dex:dexamethsone

R-CHOP: rituximab + cyclophosphamide + doxorubicin + vincristine/oncovin + prednisolone;

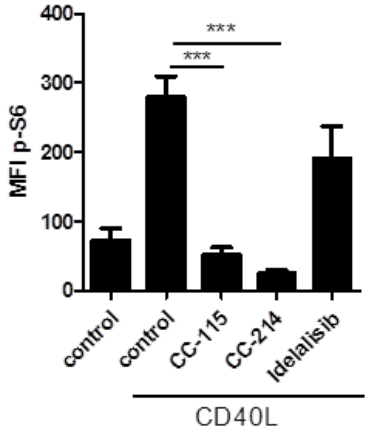
BR: bendamustine + rituximab, F:Fludarabine, R: rituximab, HDAC: histone deacetylase inhibitor

Supplemental Table 3: Primer sequences

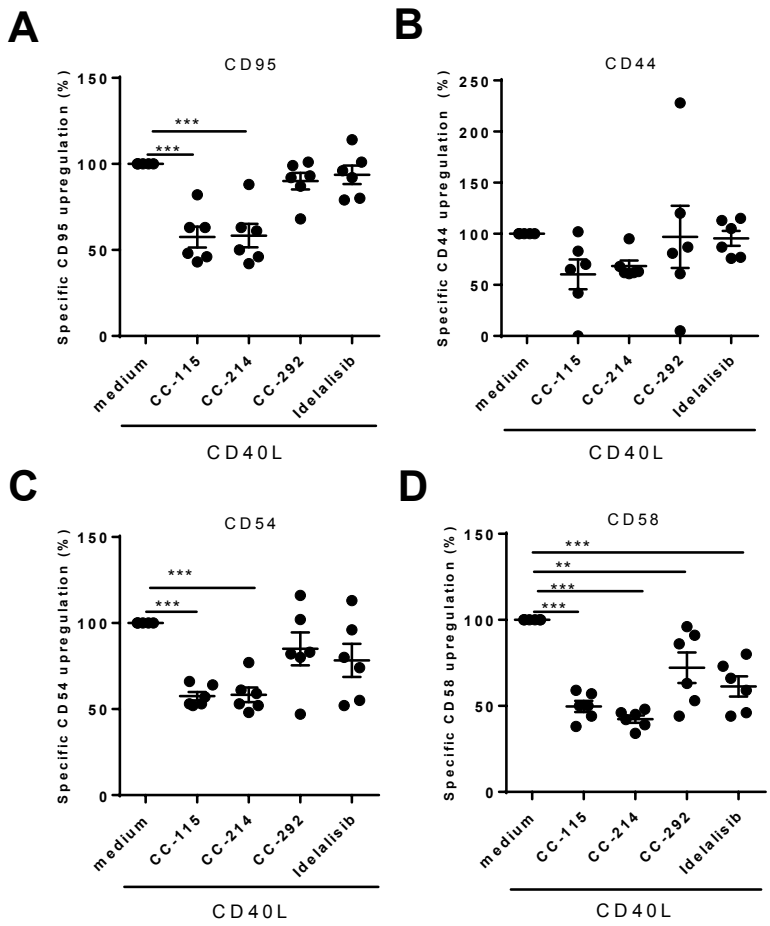
	Primer sequence
p53_exon4_Fw	5’-TGTAAAACGACGGCCAGTCTGGTAAGGACAAGGGTTGG-3’
p53_exon4_Rv	5’-CAGGAAACAGCTATGACCGATACGGCCAGGCATTGAAG-3’
p53_exon5_Fw	5’-TGTAAAACGACGGCCAGTCTAGCTCGCTAGTGGGTTGC-3’
p53_exon5_Rv	5’-CAGGAAACAGCTATGACCCACTCGGATAAGATGCTGAG-3’
p53_exon6_Fw	5’-TGTAAAACGACGGCCAGTCCACCATGAGCGCTGCTCAG-3’
p53_exon6_Rv	5’-CAGGAAACAGCTATGACCCCCTTAGCCTCTGTAAGCTTC-3’
p53_exon7_Fw	5’-TGTAAAACGACGGCCAGTGCCTCCCCTGCTTGCCACAG-3’
p53_exon7_Fw2	5’-TGTAAAACGACGGCCAGTCCTCCCCTGCTTGCCACAG-3’
p53_exon7_Rv	5’-CAGGAAACAGCTATGACCGGGAGCAGTAAGGAGATTCC-3’
p53_exon8&9_Fw	5’-TGTAAAACGACGGCCAGTTTCCTTACTGCCTCTTGCTT-3’
p53_exon8&9_Rv	5’-CAGGAAACAGCTATGACCAGAAAACGGCATTTTGAGTG-3’
p53_exon10_Fw	5’-TGTAAAACGACGGCCAGTCAATTGTAACTTGAACCATC-3’
p53_exon10_Rv	5’-CAGGAAACAGCTATGACCGGATGAGAATGGAATCCTAT-3’



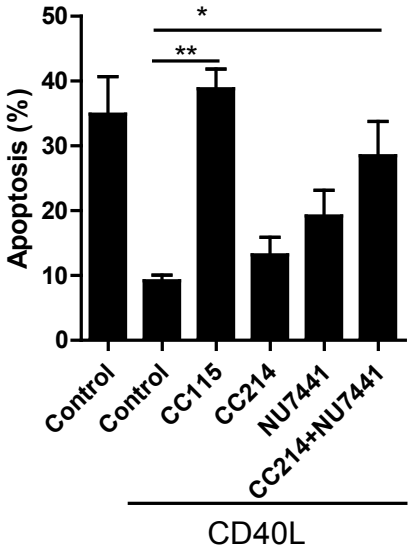
Supplemental Figure 1. CC-115 inhibits the DNA damage repair pathway in ATM wildtype and deficient cells. CLL cells were incubated with the indicated concentration CC-115 for 30 minutes and treated without (**A**) or with 10 μg/ml Bleomycin (**B**) and protein lysates were made after 30 minutes. Protein lysates were probed for pDNA-PK (S2056), DNA-PK, pATM (S1981), ATM, pHSP90α (T5/7), HSP90α, γH2AX and vinculin and cofilin for loading control. Blots from nine patients are analyzed (Supplemental table 1 CLL pt#84-92) and densitometric analysis of pDNA-PK, pATM, pHSP90α and γH2AX are shown. *p<0.05, **p<0.01, ***p<0.001 (one-way ANOVA).



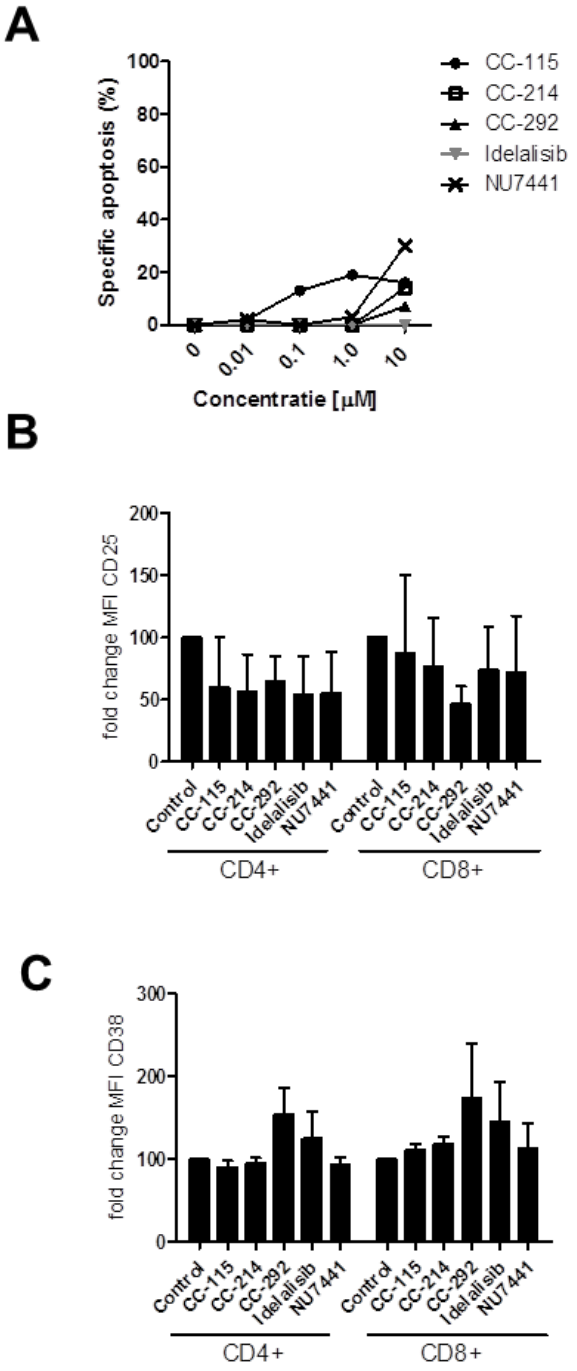
Supplemental Figure 2. CC-115 blocks pS6 expression in CLL cells. CLL cells were cultured on fibroblasts (Control) or CD40L-expressing fibroblasts (CD40L) in the presence or absence of 1 μM of the indicated drugs for 3 days. pS6 expression was analyzed by FACS. Results are shown as mean ± SEM. ***p<0.001 (one-way ANOVA) (n=8).



Supplemental Figure 3. CC-115 inhibits CD40-induced activation of CLL cells. A-D. CLL cells were cultured on 3T3 fibroblasts or CD40L-expressing fibroblasts (CD40L) in the presence or absence of 1 μM of CC-115, CC-214, CC-292 or idelalisib for 3 days. CLL cells were examined for surface expression of CD95 (Fas) (**A**), CD44 (**B**), CD54 (ICAM) (**C**) and CD58 (LFA-3) (**D**) by flow cytometry. Specific upregulation is defined as [MFI 3T40 control – MFI drug treated cells] / [MFI 3T40 control – MFI 3T3 control] x 100 using the Graphpad Prism software. Results are shown as mean ± SEM (n=6, pt#6, 19B, 21, 25, 30, 34A) (100% = stimulated cells without inhibitors). *p<0.05, **p<0.01, ***p<0.001 (one-way ANOVA).



Supplemental Figure 4. Combined mTOR and DNA-PK inhibition induces apoptosis in CD40-stimulated CLL cells. CLL cells were cultured on fibroblasts (Control) or CD40L-expressing fibroblasts (CD40L) in the presence or absence of 1 μM of the indicated drugs for 3 days. Survival was analyzed by DiOC6 staining. Results are shown as mean ± SEM. *p<0.05, **p<0.01 (one-way ANOVA)(n=3).



Supplemental Figure 5. The kinase inhibitors do not induce cell death or inhibits activation of healthy T cells. A. PBMCs from CLL patients were incubated with 0.01-10 µM of indicated drugs for 48 hours. Apoptosis was analyzed by measuring DiOC6 signal in CD3+ T cells. Specific apoptosis was calculated. **B-C.** PBMCs from healthy donors were stimulated with αCD3/αCD28 in the presence or absence of 1 µM CC-115, CC-214, CC-292, Idelalisib or NU7441 for 72 hours (n=3). **B.** CD25 expression was measured by FACS in $CD8^+$ T cells or $CD4^+$ T cells. Results are shown as mean ± SEM. ns (one-way ANOVA) **C.** CD38 expression was measured by FACS in $CD8^+$ T cells or $CD4^+$ T cells. Results are shown as mean ± SEM. ns (one-way ANOVA).