

Interleukin-1 receptor associated kinase 1/4 and bromodomain and extra-terminal inhibitions converge on NF- κ B blockade and display synergistic antitumoral activity in activated B-cell subset of diffuse large B-cell lymphoma with MYD88 L265P mutation

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SUPPLEMENTAL TABLES

Supplemental Table S1. Modulation of gene expression by IRAKi and IRAKi/CPI203 combination in DLBCL cell lines.

CUSTOM GENE SETS ¹	SIZE	IRAKi vs control		Combo vs IRAKi	
		NES	FDR q-val	NES	FDR q-val
BLIMP B-CELL REPRESSED	64	2.44	<0.0001	2.16	<0.0001
NFKB_ALL_OCILY3_LY10	58	1.76	0.007	1.99	<0.0001
NFKB_BOTHOCILY3ANDLY10	34	1.84	0.003	1.46	0.056
NFKB_K1106	17	1.62	0.013	0.93	0.705
PAX5 REPRESSED	62	1.37	0.086	-0.87	0.804
XBP1_TARGET_ALL	70	0.89	0.957	-0.93	0.737
PLASMA CELL VS B-CELL	37	-1.30	0.217	0.91	0.689
NFKB_OCILY10_ONLY	16	-1.20	0.244	1.89	0.002

¹ Raw microarray data were normalized using Expression Console Software v1.1 (Affymetrix) and gene signatures were determined with GSEA version 2.0 (Broad Institute, Cambridge, MA USA) using custom gene sets (<http://lymphochip.nih.gov/signaturedb/index.html>).

Supplemental Table S2. A selected set of NF-kB-regulated genes are differentially modulated by IRAKi/CPI203 drug combination in ABC-DLBCL cell lines with *MYD88*^{L265P}.

GENE SYMBOL	RANK METRIC SCORE			NFKB_ALL_OCILY3_LY10 CORE ENRICHMENT		
	CT vs IRAKi	IRAKi vs combo	ratio	CT vs IRAKi	CT vs CPI203	IRAKi vs combo
<i>NFKBIA</i>	-0.0496	-0.7811	15.7	-	-	-
<i>BATF</i>	0.1380	1.9920	14.4	-	Yes	Yes
<i>LTA</i>	0.0390	0.5093	13.0	-	-	Yes
<i>MARCKS</i>	0.0369	0.4726	12.8	-	-	Yes
<i>IL6</i>	0.1045	1.0530	10.1	-	Yes	Yes
<i>CD44</i>	0.0498	0.3837	7.7	-	-	Yes
<i>CFLAR</i>	0.1573	1.1140	7.1	-	Yes	Yes
<i>MX1</i>	0.1948	1.3040	6.7	-	Yes	Yes
<i>MX1</i>	0.2341	1.3320	5.7	-	Yes	Yes
<i>RASGRP1</i>	0.0655	0.2800	4.3	-	Yes	Yes
<i>IRF4</i>	0.1176	0.3699	3.1	-	-	-
<i>STAT1</i>	0.0998	0.3125	3.1	-	Yes	Yes
<i>NFKB2</i>	0.1674	0.4954	3.0	-	-	-
<i>HEATR1</i>	-0.1842	-0.5230	2.8	-	-	Yes
<i>CD83</i>	0.5992	1.5090	2.5	-	-	-
<i>SAMD9L</i>	-0.2272	-0.5635	2.5	Yes	Yes	Yes
<i>CCR7</i>	0.6529	1.5950	2.4	-	-	-
<i>TRAF1</i>	0.7852	1.7170	2.2	Yes	Yes	Yes
<i>IL12B</i>	0.3663	0.7928	2.2	Yes	Yes	Yes

SUPPLEMENTAL FIGURE LEGEND

Figure S1. (A) Single agent IRAKi fails to evoke a significant antitumoral response in an ABC-DLBCL primary xenograft model. Nine NSG mice were inoculated subcutaneously with 10^7 OCI-LY3 cells. Two weeks later, they started to be dosed daily with 1 or 5 mg/kg IRAKi (i.p., BID) or an equal volume of vehicle (n=3 animals per group) in a five/two (on/off) schedule. After 3 weeks, animals were euthanized, and tumor volumes were recorded *ex vivo*. (B) Anti-IL-6 antibody (Tocilizumab) fails to sensitize ABC-DLBCL cells to IRAKi-based treatments. Cells were exposed 24h to 20 or 50 μ M dose of IRAKi together with 5 μ g/ml Tocilizumab (Toci) showing no differences in cell death when exposed to both concentration of anti-IL-6 antibody.

SUPPLEMENTAL FIGURE

FIGURE S1

