

### **Supplementary Table 1**

Details of the antibodies used for flow cytometry and immunoblotting.

### **Supplementary Figure 1**

(A) Dose responses for IBL-202 and venetoclax in combination at a ratio of 1 : 100 against primary CLL cells co-cultured with CD40L-expressing fibroblasts (n = 10).

(B) Combination index (CI) plot (left) and isobologram (right) for IBL-202 and venetoclax in combination indicating synergy between the drugs against CLL patient samples (n = 6) when in co-culture with HS-5 stromal cells (n = 6). CI values < 1 are indicative of synergy. The data are presented as the CI over a range of fractional effects where a Fe value of 0.5, for example, is indicative of a 50% cell kill.

(C) Histogram showing the Bax/Bcl-2 expression ratio in CLL patient samples (n = 6) following treatment with IBL-202 and venetoclax, alone and in combination.

(D) Dose response of wild-type (WT) and pre-doxycycline treated, Cas9 / *TP53*-targeted guide RNA OSU-CLL cells (Cas9 + gRNA) treated with IBL-202 alone, or in combination with venetoclax. Cell viability was assessed by flow cytometry and DiIC<sub>1</sub>(5)/PI following a 48-h treatment. Doses of IBL-202 are indicated on the X-axis. Venetoclax and IBL-202 were combined at a ratio of 1 : 5.

(E) Electropherogram illustrating sequencing results of the *TP53* genetic region from wild-type and *TP53*ko OSU-CLL lines. Western blotting for p53 protein expression in WT and *TP53*ko OSU-CLL cells with and without treatment with etoposide (50  $\mu$ M, 6 h), indicating that induction of DNA strand breaks upregulates p53 expression in WT but not *TP53*ko OSU-CLL cells.

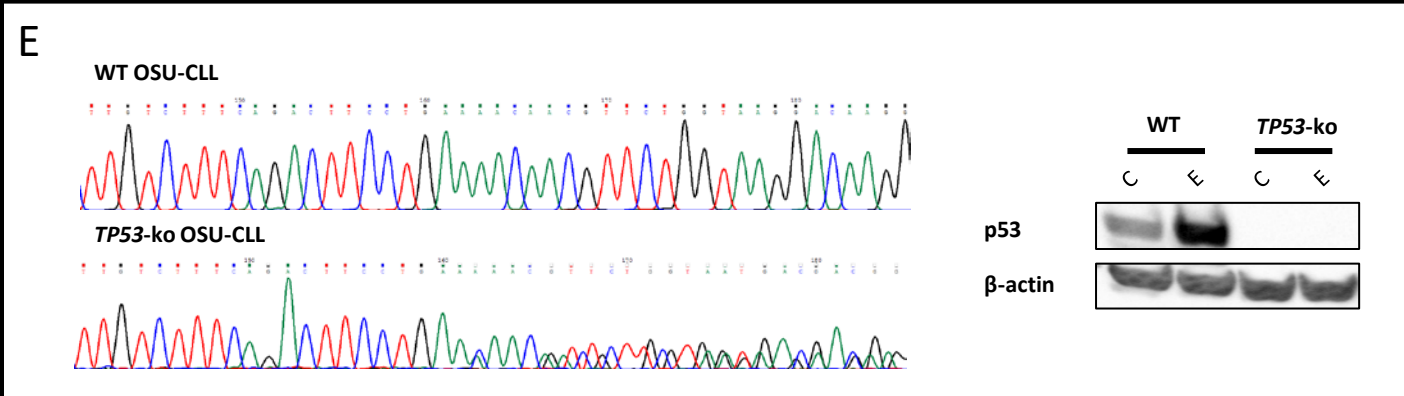
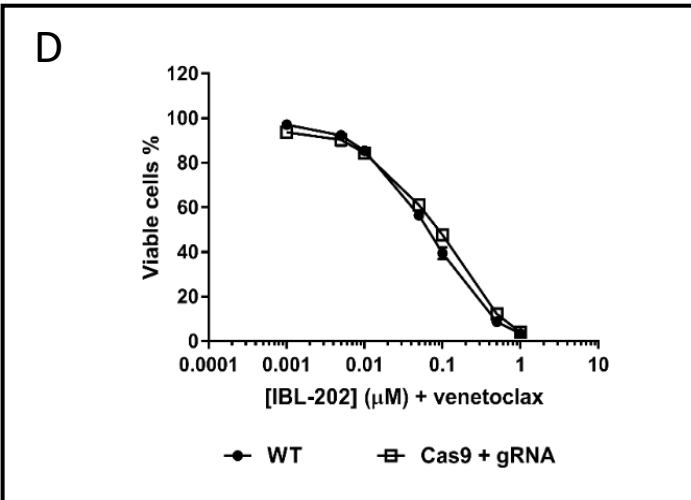
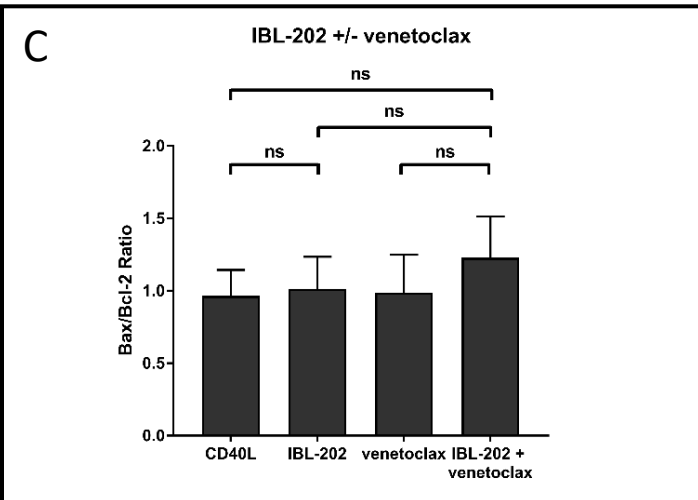
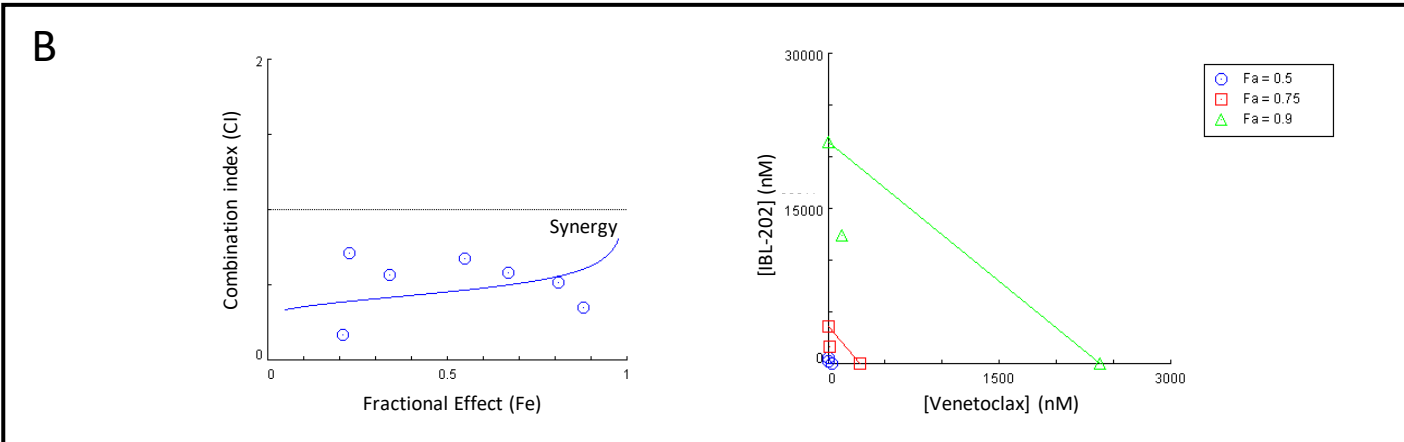
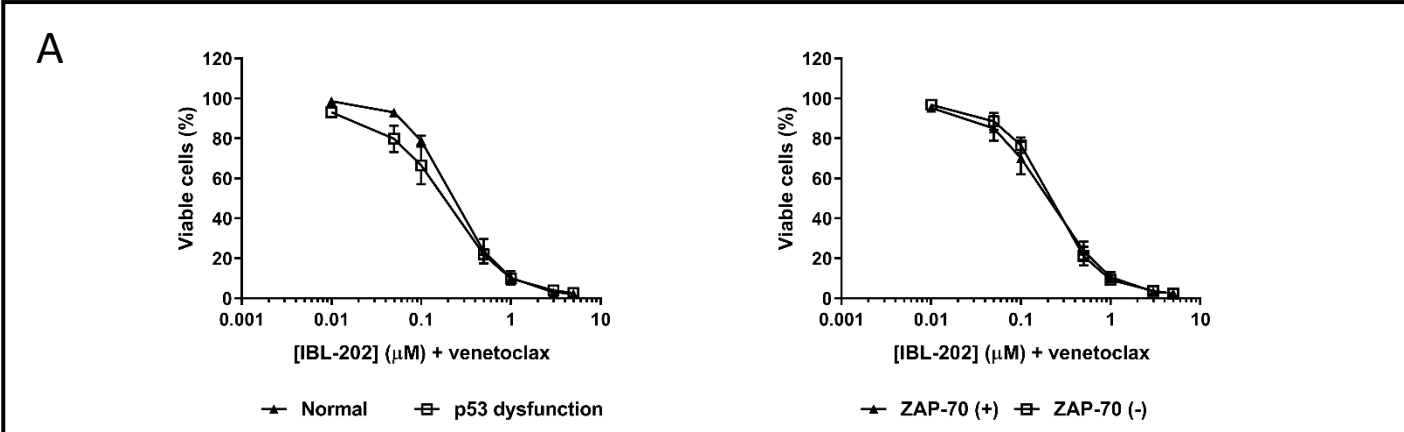
### **Supplementary Figure 2**

Changes in the expression of the proteins indicated following treatment with IBL-202 and venetoclax, alone or in combination for 6h, were examined in CLL patient samples (n = 5) co-cultured with CD40L-fibroblasts. The first lane in each panel is an untreated control of CLL cells cultured in medium alone with no drug treatment. The values shown under each lane indicate the fold change in expression relative to the untreated control for each patient.

**Supplementary Table 1. antibody information**

<b>Antibody</b>	<b>Clone</b>	<b>Catalogue #</b>	<b>Manufacturer</b>	<b>Phosphorylation site</b>
phospho-AKT	D9E	4060	CST	Ser473
AKT	C67E7	4691	CST	
phospho-NFκB	93H1	3033	CST	Ser536
NFκB	L8F6	6956	CST	
phospho-Bad	40A9	5284	CST	Ser112
Bad	D24A9	9239	CST	
Bcl-xL	54H6	2764	CST	
Mcl-1	D2W9E	94296	CST	
Noxa	D8L7U	14766	CST	
Bcl-2	D55G8	4223	CST	
Bax	D2E11	5023	CST	
c-Myc	D84C12	5605	CST	
Cleaved PARP	Asp214	9541	CST	
β-actin	AC-74	A5316	Sigma-Aldrich	
PE-CD49d	9F10	304304	BioLegend	
PE-CXCR4(CD184)	12G5	306506	BioLegend	
FITC-CD5	UCHT2	300606	BioLegend	
APC-CD19	HIB19	302212	BioLegend	

Supplementary Figure 1.



# Supplementary Figure 2.

