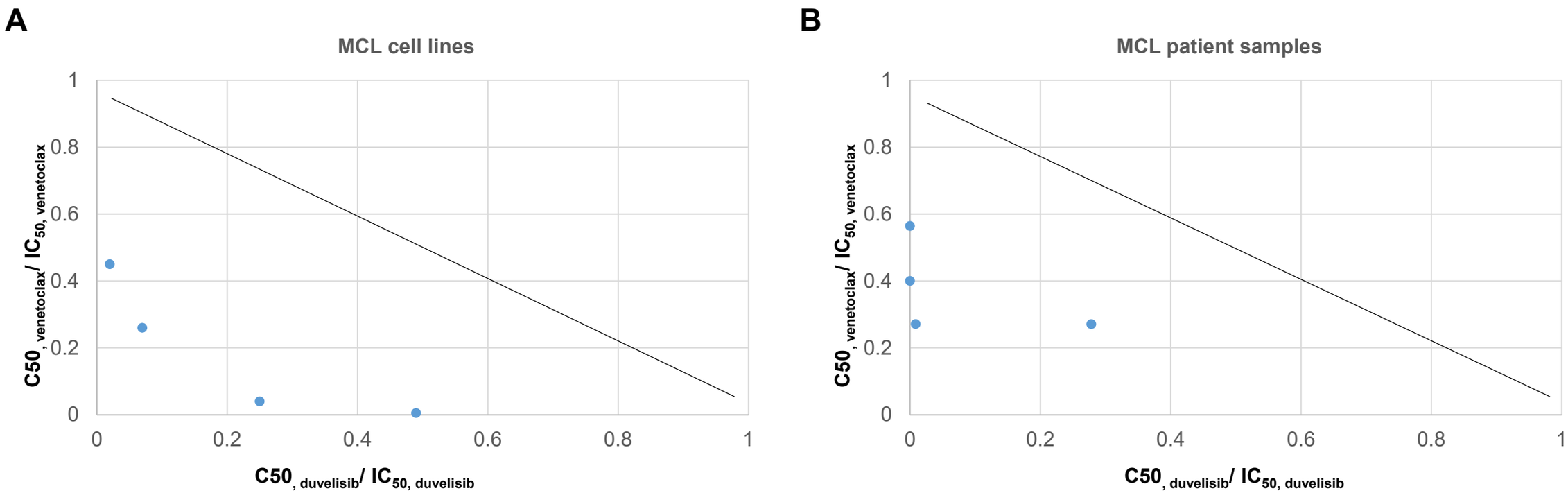
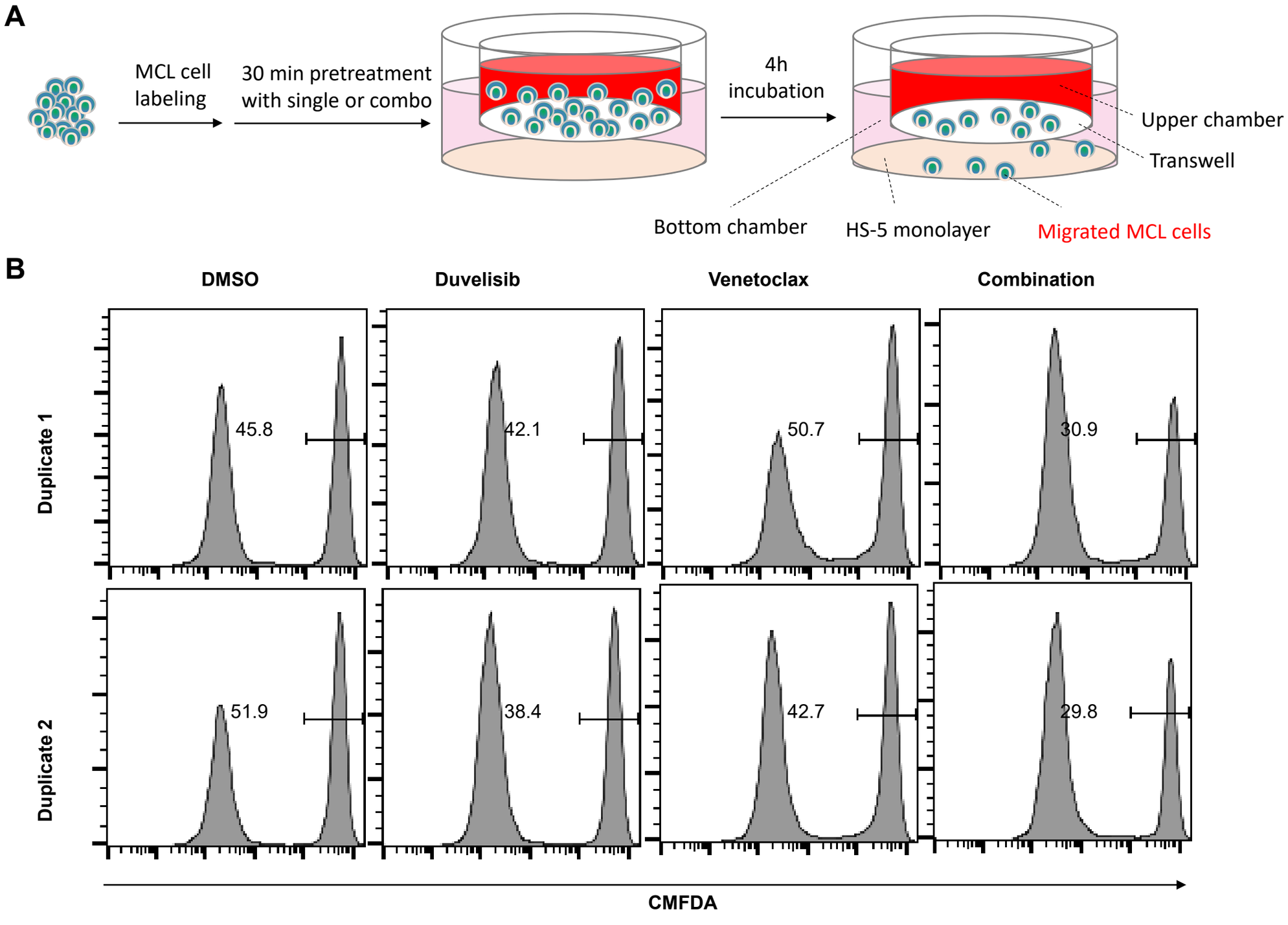
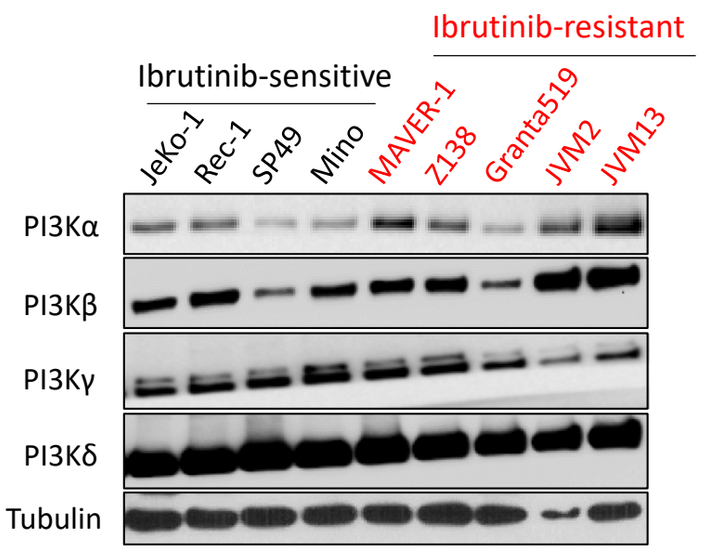
Supplementary figures and legends



Supplementary Figure S1. Isobologram analysis for combinational effect of duvelisib and venetoclax in MCL cell lines (n = 4) (A) and primary patient samples (n = 4) (B).



Supplementary Figure 2: Duvelisib and venetoclax combination showed greater inhibition in TME-mediated cell migration *in vitro*. (**A**) Schematic design for *in vitro* MCL cell migration. Ibrutinib-resistant JeKo BTK KD cells were stained with CellTracker™ Green CMFDA Dye and pretreated with DMSO, duvelisib at 5 µM, venetoclax at 100 nM, alone or in combination, for 30 minutes and washed with 1x PBS before adding to the upper chamber for the trans-well migration assay. The bottom chamber was pre-seeded with human stroma cell lines HS-5 overnight. The trans-well systems were incubated for 4 hours before collection of migrated MCL cells and flow cytometry analysis. (**B**) Migrated MCL cells were detected by flow cytometry based on CMFDA-labeling. Representative flow cytometry data are shown. The CMFDA-positive cells (the right peak) represent the migrated MCL cells into the lower chamber that were CMFDA-labelled before loading into the upper chamber, and the negative cells (the left peak) represent the HS-5 cells which were not labeled with CMFDA.



Supplementary Figure S3: Expression of PI3K isoforms in ibrutinib-sensitive (black) and –resistant (red) MCL cell lines.

Supplementary Table S1. Clinical characteristics of patients with MCL.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Sex	M	M	F	M
Age	75	69	70	50
Bone marrow involvement	Positive	Negative	Positive	low
Peripheral blood involvement	Positive	Positive	Positive	Positive
Karyotype	Complex	Normal	Complex	Normal
TP53	NA	Positive	NA	NA
Ki67	20%	>95%	65%	40-50%
Sox11	NA	Positive	Positive	NA
Histology type	Blastoid	Blastoid	Blastoid	classic
Prior therapy	1	1	1	2
BTKi therapy	Acalabrutinib	Ibrutinib	Ibrutinib	Ibrutinib
Response to BTKi therapy	Relapsed	Relapsed	Relapsed	Relapsed
Ibrutinib-resistant	Yes	Yes	Yes	Yes