Supplementary Methods

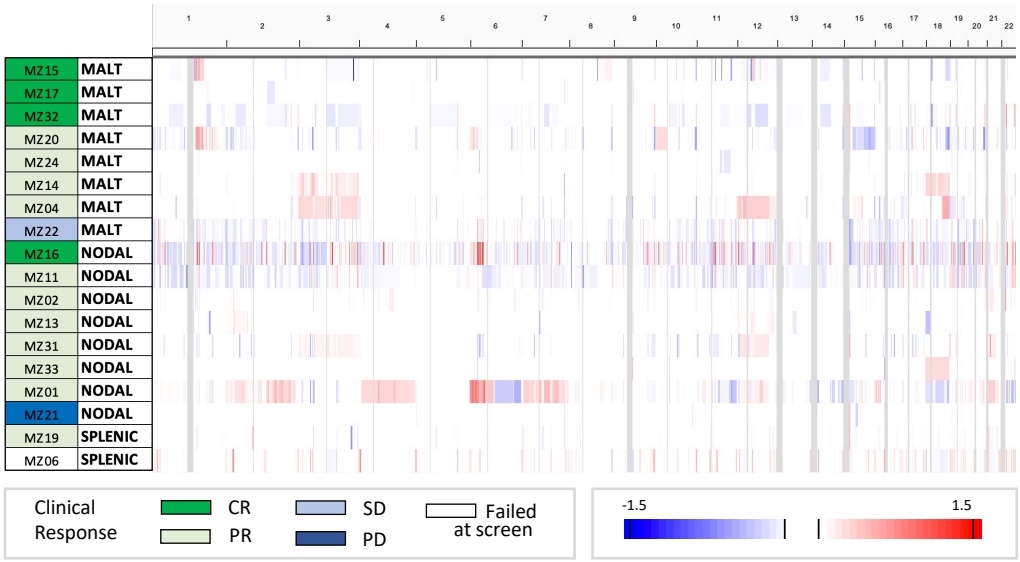
NGS library manufacture: DNA input for NGS library preparation was 45 to 50 ng. For cfDNA, this quantity was harvested from (on average) 8 mL STRECK plasma (i.e., two STRECK® blood collection tubes). Quality metrics on input DNA and library preparation was performed using Bioanalyzer or Agilent TapeStation reagents (Agilent Technologies, CA, USA).

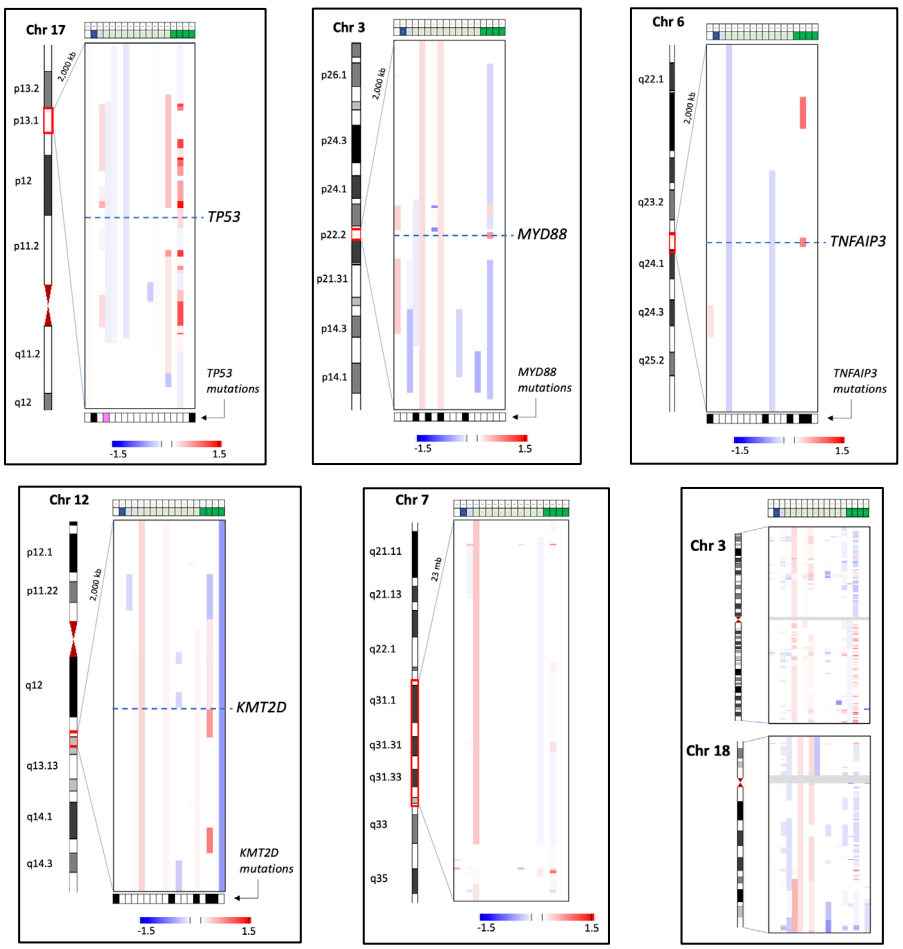
Bioinformatic analysis: for WES analysis, mutations were discarded if they did not meet the following pre-specified criteria from *VarDict* output: quality score ≥60, p-mean ≥19.5, odds ratio 1-1.5, variant read depth ≥6 (reference to alternate 3:3) and variant allele frequency (VAF) ≥5%.[1] For mutations detected with VAF <5%, quality score cut-off was increased to ≥100. Mutations with VAF<3% were discarded. For samples without a germline comparator, a population frequency of ≥1% as per Genome Aggregation databases (Gnomad, ESP6500, as accessed via OpenCRAVAT was deemed a likely population single nucleotide polymorphism and therefore excluded.[2] The same curation rules were applied for the purposes of ctDNA analysis, although a VAF cut-off of ≥0.2% was used, or ≥0.1% if the mutation was present in the corresponding tumour sample or at a known hotspot (e.g., *MYD88* L265P).

BTK structural model: Human BTK kinase is a multi-domain protein composed of Pleckstrin-homology (PH) domain, Tec-homology (TH) domain, two Src-homology (SH) domains SH3 – SH2 and kinase domain. In order to explore spatial relationship between the zanubrutinib binding site and E41K mutation, the experimental structures of the separate domains of human BTK: PH-TH domain of human BTK (RCSB PDB: 1BWN), SH2 domain (RCSB PDB: 2GE9) and the kinase domain in complex with zanubrutinib (RCSB PDB: 6J6M) were superimposed on the theoretical model of full length BTK downloaded from the SWISS-MODEL server. This model of full length human BTK, in turn, is based on the construct PH-Kinase domain from bovine BTK crystal structure (RCSB PDB: 4Y93).

References:

1. Lai Z, Markovets A, Ahdesmaki M, et al. VarDict: a novel and versatile variant caller for next-generation sequencing in cancer research. *Nucleic Acids Res*. 2016;44(11):e108.
2. Pagel KA, Kim R, Moad K, et al. Integrated Informatics Analysis of Cancer-Related Variants. *JCO Clin Cancer Inform*. 2020;4:310-317.





Supplementary Figure 1. CNV analysis from WES data. CNVkit was used to evaluate copy number changes for the 18 primary tumors investigated by WES. Data presented with corresponding histology type and zanubrutinib response. Enlarged regions shown for *TP53*, *MYD88*, *KMT2D*, *TNFAIP3*, Chromosome 7 q31-31 and (combined) Chromosome 3 and 18.

ARID3A	*DNAH10*	*IL20RA*	*NOTCH2*
ATM	*DTX1*	*ITCH*	*PLCG2*
BCL10	*EP300*	*KLF2*	*PRKDC*
BIRC3	*FAS*	*KLHL6*	*PTPRD*
BTK	*FAT1*	*KMT2D*	*RBPJL*
CACNA1H	*FAT3*	*MAML2*	*REL*
CARD11	*FAT4*	*MAP3K14*	*SPEN*
CCND3	*FBXO11*	*MYD88*	*SWAP70*
CD79A	*FBXW7*	*NCOR2*	*TBL1XR1*
CD79B	*GPS2*	*NFKB1*	*TNFAIP3*
CREBBP	*IGLL5*	*NFKBIA*	*TP53*
CXCR4	*IKBKB*	*NOTCH1*	*TRAF3*

Supplementary Table 1. Candidate genes.

Study ID	Age	Sex	Subtype	Prior lines of therapy	Tumour sample site	Best response	Progression	PFS (months)
MZ01	71	M	NODAL	2	Lymph node	PR	N	16.54
MZ02	64	M	NODAL	2	Bone marrow trephine	PR	N	11.51
MZ04	80	F	MALT	3	Lung	PR	N	16.37
MZ06	86	F	SPLENIC	2	Bone marrow trephine	Screen fail	NA	NA
MZ11	78	M	NODAL	1	Lymph node	PR	N	16.34
MZ13	52	F	NODAL	2	Lymph node	PR	N	11.05
MZ14	61	M	MALT	1	Soft tissue (right triceps)	PR	N	16.57
MZ15	72	M	MALT	1	Soft tissue (lacrimal gland)	CR	N	10.95
MZ16	71	M	NODAL	1	Soft tissue (left trapeze)	CR	N	10.85
MZ17	37	M	MALT	1	Stomach, Lymph node	CR	N	16.80
MZ19	81	F	SPLENIC	3	Skin	PR	Y	5.33
MZ20	83	M	MALT	1	Soft tissue (Orbital)	PR	Y	8.68
MZ21	68	F	NODAL	4	Lymph node	PD	Y	2.76
MZ22	72	M	MALT	2	Stomach	SD	Y	11.08
MZ24	68	F	MALT	1	Bone marrow aspirate	PR	N	16.73
MZ31	65	M	NODAL	1	Lymph node	PR	N*	13.40
MZ32	82	M	MALT	2	Lung	CR	N	10.88
MZ33	40	M	NODAL	1	Lymph node	PR	N	11.05

*COVID-19 related death

Supplementary Table 2. Characteristics of patients who underwent WES of tumor sample.