Olverembatinib in accelerated-phase chronic myeloid leukemia: efficacy and safety evaluation

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Received: May 15, 2025.
Accepted: October 3, 2025.
Early view: October 16, 2025.

https://doi.org/10.3324/haematol.2025.288249

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Supplement information

Supplement Method

Targeted DNA sequencing

DNA was obtained from cryopreserved mononuclear cells of blood using QIAsymphony SP (QIAGEN, Germany) or dsDNA HS Assay Kit (Life Technologies, Darmstadt, Germany). Buccal mucosa sample was used as a non-malignant control to identify the germline background variants. Targeted DNA sequencing was performed using well validated laboratory designed hematologic tumor panels to capture exons and splice sites of genes in hematologic malignancies at two College of American Pathologists (CAP)-accredited testing laboratories. Sequencing was performed on Illumina platform (ILLUMINA, US) with average coverage depths between 1200x to 2000x. The data were first demultiplexed and the FASTQ file was subjected to quality control to remove low-quality data or N bases. Qualified reads were mapped to the reference human genome, hg19, using the Burrows-Wheeler Aligner. The Genome Analysis Toolkit (GATK 3.4.0) was used to perform local realignment around indels and base quality score re-calibration. Picard was used to remove PCR duplicates. VarScan2 was used for the detection of single-nucleotide variants and insertion/deletion variants. A variant allele frequency cutoff of 1.0% was used for SNVs and Indels.

Supplement Table 1. Targeted gene list in Nanjing Geneseeq Technology.

ABCB1	CCND3	ECT2L	HDAC2	MED12	POLE	SRC
ABCC2	CCNE1	EED	HDAC4	MEF2B	POT1	SRP72
ABL1	CCR4	EGFR	HDAC7	MEN1	POU2AF1	SRSF2
ABL2	CCT6B	EGR1	HGF	MET	PPM1D	SRY
ACTB	CD22	EML4	HIST1H1	MFHAS1	PPP2R1A	STAG2
ADH1B	CD274	EP300	HNF1A	MGA	PRDM1	STAT3
AIM1	CD28	EPCAM	HNF1B	MGMT	PRF1	STAT5A
AIP	CD58	EPHA2	HRAS	MITF	PRKAR1A	STAT5B
AKT1	CD70	EPHA3	HSD3B1	MLH1	PRKCB	STAT6
AKT2	CD74	ERBB2	ID3	MLH3	PTCH1	STIL
AKT3	CD79A	ERBB3	IDH1	MPL	PTEN	STK11
ALDH2	CD79B	ERBB4	IDH2	MRE11A	PTPN1	STMN1
ALK	CD83	ERCC1	IGF1R	MSH2	PTPN11	STT3A
ANKRD26	CDA	ERCC2	IKBKE	MSH3	PTPN13	STX11
AP3B1	CDC73	ERCC3	IKZF1	MSH6	PTPN2	STXBP2
APC	CDH1	ERCC4	IKZF2	MTHFR	PTPN6	SUFU
AR	CDK10	ERCC5	IKZF3	MTOR	PTPRD	SUZ12
ARHGAP2	CDK12	ERG	IL7R	MUTYH	PTPRK	SYK
ARID1A	CDK4	ESR1	INPP4B	MYC	PTPRO	TAL1
ARID1B	CDK6	ETNK1	INPP5D	MYCL	RAB27A	TBL1XR1
ARID2	CDK8	ETS1	IRF1	MYCN	RAC3	TBX21
ARID5B	CDKN1B	ETV1	IRF4	MYD88	RAD21	TCF3
ASXL1	CDKN1C	ETV4	IRF8	MYH11	RAD50	TCL1A
ASXL2	CDKN2A	ETV6	ITPKB	NAT1	RAD51	TEK
ASXL3	CDKN2B	EWSR1	JAK1	NBN	RAF1	TEKT4
ATG5	CDKN2C	EZH2	JAK2	NCSTN	RARA	TERT
ATM	CEBPA	FANCA	JAK3	NF1	RASGEF1	TET2
ATR	CEP57	FANCC	JARID2	NF2	RB1	TGFBR2
ATRX	CHD8	FANCD2	JUN	NFKB1	RECQL4	TLE1
AURKA	CHEK1	FANCE	KDM2B	NFKB2	REL	TLE4
AURKB	CHEK2	FANCF	KDM5A	NFKBIA	RELN	TMPRSS2
AXIN1	CIITA	FANCG	KDM5C	NFKBIE	RET	TNFAIP3
AXL	CKS1B	FANCL	KDM6A	NKX2-1	RHOA	TNFRSF11
B2M	CMTM6	FAS	KDR	NOTCH1	RICTOR	TNFRSF14
BAP1	CREBBP	FAT1	KIF5B	NOTCH2	RNF43	TNFRSF17
BARD1	CSF1R	FAT4	KIR2DL4	NPM1	ROS1	TNFRSF19
BCL10	CSF3R	FBXO11	KIR3DL2	NQO1	RPTOR	TOP1
BCL11B	CTCF	FBXW7	KIT	NRAS	RRM1	TOP2A

BCL2	CTLA4	FGFR1	KLF2	NSD1	RUNX1	TP53
BCL2L1	CTNNB1	FGFR2	KLHL6	NT5C2	RUNX1T1	TP63
BCL2L11	CUX1	FGFR3	KLLN	NTRK1	RUNX3	TP73
BCL2L2	CXCR4	FGFR4	KLRC1	NTRK3	SBDS	TPMT
BCL6	CYLD	FH	KLRC2	NUP98	SDC4	TRAF2
BCL7A	CYP19A1	FIP1L1	KLRK1	P2RY8	SDHA	TRAF3
BCOR	CYP2A6	FLCN	KMT2A	PAG1	SDHB	TRAF5
BCORL1	CYP2B6*6	FLT1	KMT2B	PAK3	SDHC	TSC1
BCR	CYP2C19*	FLT3	KMT2C	PALB2	SDHD	TSC2
BIRC3	CYP2C9*3	FLT4	KMT2D	PAX5	SERP2	TSHR
BIRC5	CYP2D6	FOXO1	KRAS	PBRM1	SETBP1	TTF1
BLM	CYP3A4*4	FOXO3	LAMP1	PC	SETD2	TUBB3
BMPR1A	CYP3A5*3	FYN	LEF1	PDCD1	SF3B1	TYMS
BRAF	DAXX	GADD45	LMO1	PDCD1LG	SGK1	U2AF1
BRCA1	DDR2	GATA1	LMO2	PDE11A	SH2B3	UGT1A1
BRCA2	DDX3X	GATA2	LYN	PDGFRA	SH2D1A	UNC13D
BRD4	DDX41	GATA3	LYST	PDGFRB	SLC34A2	VEGFA
BRIP1	DHFR	GNA11	MAF	PDK1	SLC7A8	VHL
BTG1	DHX15	GNA13	MAFB	PGR	SMAD2	WHSC1
BTG2	DICER1	GNAQ	MALT1	PHF6	SMAD4	WT1
BTK	DNM2	GNAS	MAP2K1	PHOX2B	SMAD7	XIAP
BTLA	DNMT3A	GRIN2A	MAP2K2	PIK3CA	SMARCA4	XPC
BUB1B	DNMT3B	GSTM1	MAP2K4	PIK3CD	SMARCB1	XPO1
CALR	DOT1L	GSTP1	MAP3K1	PIK3R1	SMC1A	XRCC1
CARD11	DPYD	GSTT1	MAP3K14	PIK3R2	SMC3	YAP1
CBFB	DTX1	HACE1	MAP4K3	PIM1	SMO	ZAP70
CBL	DUSP2	HBA1	MAPK1	PLCG2	SOCS1	ZBTB7A
CBLB	DUSP22	HBA2	MCL1	PML	SOX2	ZNF2
CCND1	EBF1	HBB	MDM2	PMS1	SPEN	ZRSR2
CCND2	ECSIT	HDAC1	MDM4	PMS2	SPOP	-
Rearrangement in genomic hotspots						
IGH	IGL	IGK	TRB	TRA	TRG	-

Supplement Table 2. Uni-variable analyses results of therapy responses and outcomes.

Co-variates	CCyR		MMR		MR4.0		TFS		CML-related survival		Survival	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Age, year	0.9 (0.8, 1.1)	0.390	1.0 (0.8, 1.2)	0.819	0.9 (0.7, 1.2)	0.395	0.7 (0.5, 1.0)	0.065	1.1 (0.8, 1.5)	0.766	1.2 (0.9, 1.6)	0.163
Male sex (ref. female)	1.2 (0.6, 2.1)	0.622	1.1 (0.6, 2.0)	0.814	0.9 (0.4, 1.9)	0.797	1.1 (0.4, 3.1)	0.864	1.4 (0.5, 3.8)	0.563	1.4 (0.6, 3.6)	0.450
Comorbidity(ies) (ref. none)	0.8 (0.5, 1.5)	0.536	0.6 (0.3, 1.2)	0.143	0.4 (0.2, 1.0)	0.050	0.9 (0.3, 2.7)	0.903	1.1 (0.4, 2.8)	0.900	1.4 (0.6, 3.1)	0.463
Accelerated phase at diagnose (ref. Chronic phase)	1.6 (0.9, 2.9)	0.105	1.5 (0.8, 1.8)	0.126	1.3 (0.9, 1.6)	0.095	1.2 (0.5, 3.1)	0.699	1.0 (0.3, 3.0)	0.990	1.0 (0.4, 2.6)	0.952
Interval from diagnosis to olverembatinib start, mo (continuous)	0.9 (0.8, 0.9)	<0.001	0.9 (0.8, 0.9)	<0.001	0.9 (0.8, 1.0)	0.001	0.9 (0.8, 1.0)	0.026	1.0 (0.9, 1.1)	0.864	1.0 (0.9, 1.1)	0.902
Number of prior TKIs >2 (ref. ≤ 2)	0.8 (0.5, 1.4)	0.426	0.7 (0.4, 1.3)	0.253	0.9 (0.5, 1.8)	0.818	0.8 (0.3, 2.2)	0.649	0.5 (0.2, 1.5)	0.218	0.6 (0.3, 1.6)	0.328
Best prior TKI-therapy responses*	3.3 (1.9, 5.9)	<0.001	4.3 (2.4, 7.9)	<0.001	5.6 (2.7, 11,4)	<0.001	0.5 (0.2, 1.3)	0.163	0.5 (0.2, 1.3)	0.149	0.4 (0.2, 0.9)	0.020
Clinical trials (ref. Off-study)	0.8 (0.5, 1.4)	0.516	1.0 (0.6, 1.8)	0.979	1.0 (0.5, 2.0)	0.987	1.6 (0.6, 4.5)	0.366	1.1 (0.4, 3.0)	0.899	1.1 (0.5, 2.8)	0.783
Accelerated phase at the start of olverembatinib therapy (ref. 2nd chronic phase)	0.7 (0.4, 1.2)	0.227	0.9 (0.5, 1.5)	0.657	0.8 (0.4, 1.5)	0.501	1.2 (0.5, 3.1)	0.699	4.1 (1.4, 12.5)	0.012	3.3 (1.3, 8.3)	0.012
WBC (×10E + 9/L)	1.1 (0.9, 1.2)	0.324	1.0 (1.0, 1.2)	0.302	1.1 (1.0, 1.2)	0.043	0.9 (0.6, 1.2)	0.482	1.0 (0.8, 1.2)	0.794	0.9 (0.7, 1.2)	0.567
Haemoglobin (g/L)	1.1 (1.0, 1.2)	0.098	1.1 (0.9, 1.2)	0.402	1.1 (1.0, 1.2)	0.108	0.8 (0.7, 1.0)	0.059	0.7 (0.6, 0.8)	<0.001	0.7 (0.6, 0.8)	<0.001
Platelets (×10E + 9/L)	1.0 (1.0, 1.1)	0.205	1.0 (1.0, 1.1)	0.182	1.0 (0.9, 1.1)	0.731	0.9 (0.8, 1.1)	0.466	1.0 (0.9, 1.1)	0.696	1.0 (0.9, 1.1)	0.865
Blood and/or bone marrow blasts (%)	0.6 (0.3, 1.2)	0.149	0.6 (0.3, 1.2)	0.135	0.6 (0.2, 1.5)	0.265	2.0 (1.0, 4.2)	0.062	2.4 (1.3, 4.7)	0.007	2.1 (1.1, 4.1)	0.029
Basophils (%)	1.1 (0.9, 1.3)	0.370	1.1 (0.9, 1.3)	0.221	1.0 (0.8, 1.2)	0.767	1.0 (0.7, 1.4)	0.793	1.2 (0.9, 1.6)	0.190	1.2 (0.9, 1.5)	0.280
High-risk ACAs (ref. no)	0.5 (0.2, 1.2)	0.107	0.6 (0.3, 1.4)	0.284	0.7 (0.3, 1.9)	0.493	1.3 (0.4, 3.9)	0.675	2.1 (0.8, 5.4)	0.143	2.3 (1.0, 5.3)	0.059
Baseline *BCR::ABL1* mutation status (ref. Single *T315I* mutation)		0.035		0.011		0.094		0.969		0.611		0.919
T315I + another mutations	0.5 (0.2, 1.0)	0.058	0.4 (0.2, 0.8)	0.016	0.4 (0.1, 1.0)	0.056	1.0 (0.3, 3.6)	0.966	2.0 (0.7, 5.8)	0.193	1.3 (0.5, 3.4)	0.609
Non-*T315I* mutations	0.5 (0.2, 1.2)	0.135	0.6 (0.2, 1.3)	0.188	0.8 (0.3, 2.1)	0.683	1.4 (0.4, 5.0)	0.645	1.6 (0.4, 6.0)	0.500	1.0 (0.3, 3.4)	0.961

No mutation	0.3 (0.1, 0.9)	0.024	0.2 (0.1, 0.7)	0.013	0.3 (0.1, 1.1)	0.066	1.0 (0.2, 4.5)	0.974	1.2 (0.2, 5.4)	0.859	0.8 (0.2, 3.4)	0.723
Dose ≥ 40 mg QOD (ref. ≤ 30 mg QOD)	1.3 (0.7, 2.4)	0.346	1.2 (0.7, 2.2)	0.552	1.8 (0.8, 4.1)	0.168	1.4 (0.5, 4.3)	0.568	1.6 (0.5, 4.7)	0.429	2.0 (0.7, 6.0)	0.195
Achieving MCyR within 3 months of olverembatinib (ref. failure)	-	-	-	-	-	-	0.2 (0.1, 0.7)	0.025	0.2 (0.1, 0.8)	0.027	0.5 (0.2, 1.3)	0.178

ACAs, additional cytogenetic abnormalities; CCyR, complete cytogenetic response; CHR, complete haematologic response; CML, chronic myeloid leukemia; CI, confidence interval; HR, hazard ratio; MCyR, major cytogenetic response; mo, months; MMR, major molecular response; MR4.0, molecular response 4.0; QOD, every other day; TFS, transformation-free survival; TKI, tyrosine kinase inhibitor.

*For CCyR, MMR, or MR4.0, best prior TKI-therapy responses ≥ CCyR *versus* < CCyR; for TFS, CML-realted survival, or survival, best prior TKI-therapy responses ≥ CHR *versus* < CHR.

The co-variate “Achieving MCyR within 3 months of olverembatinib (ref. failure)” was only included in the uni-variable and multi-variable Cox models for TFS, CML-related survival, and survival.

Supplement Table 3. Multi-variable Cox analyses results of responses and outcomes in subjects with available samples by targeted DNA sequencing.

Co-variates	CCyR		MMR		MR4.0		TFS		CML-related survival		Survival	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age, year	-	-	-	-	-	-	-	-	-	-	-	-
Male sex (ref. female)	-	-	-	-	0.2 (0.1, 0.6)	0.002	-	-	-	-	-	-
Comorbidity(ies) (ref. none)	-	-	-	-	-	-	-	-	-	-	-	-
Accelerated phase at diagnose (ref. Chronic phase)	-	-	-	-	-	-	-	-	-	-	-	-
Interval from diagnosis to olverembatinib start, month(continuous)	0.9 (0.8, 0.9)	0.001	0.9 (0.8, 1.0)	0.004	0.9 (0.8, 1.0)	0.004	0.8 (0.7, 0.9)	0.003	-	-	-	-
Number of prior TKIs >2 (ref. ≤ 2)	-	-	-	-	-	-	-	-	-	-	0.2 (0.1, 0.8)	0.028
Clinical trials (ref. Off-study)	-	-	-	-	-	-	-	-	-	-	-	-
Accelerated phase at the start of olverembatinib therapy (ref. 2nd chronic phase)	-	-	-	-	-	-	-	-	-	-	-	-
WBC (×10E + 9/L)	-	-	-	-	-	-	-	-	-	-	-	-
Hemoglobin (g/L)	-	-	-	-	-	-	-	-	0.6 (0.5, 0.8)	<0.001	0.7 (0.6, 0.9)	0.008
Platelets (×10E + 9/L)	-	-	-	-	-	-	-	-	-	-	-	-
Blood and/or bone marrow blasts (%)	-	-	-	-	-	-	-	-	-	-	3.3 (1.5, 7.3)	0.002
Basophils (%), median (range)	-	-	-	-	-	-	-	-	-	-	-	-
High-risk ACAs (ref. no)	-	-	-	-	-	-	-	-	3.5 (1.1, 10.8)	0.028	-	-
Dose ≥ 40mgQOD (ref. ≤ 30mgQOD)	-	-	-	-	-	-	-	-	-	-	-	-
Achieving MCyR within 3 months of olverembatinib (ref. Failure to achieve)	-	-	-	-	-	-	0.2 (0.1, 0.8)	0.030	-	-	-	-
Best prior TKI-therapy responses*	3.7 (1.6, 8.5)	0.002	6.7 (2.7, 16.4)	<0.001	17.2 (5.3, 55.5)	<0.001	-	-	-	-	0.2 (0.1, 0.7)	0.005
Baseline *BCR::ABL1* mutation status		0.018		0.001		0.013	-	-	-	-	-	-

(ref. Single *T315I* mutation)												
T315I + another mutations	0.3 (0.1, 0.9)	0.033	0.2 (0.1, 0.7)	0.008	0.3 (0.1, 1.1)	0.064	-	-	-	-	-	-
Non-*T315I* mutations	0.4 (0.1, 1.4)	0.147	0.3 (0.1, 1.2)	0.090	0.6 (0.1, 2.8)	0.550	-	-	-	-	-	-
No mutation	0.2 (0.1, 0.7)	0.016	0.2 (0.1, 0.3)	0.001	0.1 (0.1, 0.3)	0.003	-	-	-	-	-	-
Number of non-*ABL1* somatic variant ≥ 3 (ref. < 3)	0.4 (0.2, 0.8)	0.010	-	-	-	-	-	-	2.8 (1.0, 7.7)	0.042	-	-
ASXL1 variant (ref. wt)	-	-	-	-	-	-	-	-	-	-	-	-
KMT2C variant (ref. wt)	-	-	-	-	-	-	-	-	-	-	-	-
RUNX1 variant (ref. wt)	#	#	#	#	#	#	9.4 (2.7, 33.2)	<0.001	-	-	-	-
DNMT3A variant (ref. wt)	-	-	-	-	-	-	/	/	-	-	-	-
IKZF1 variant (ref. wt)	-	-	-	-	-	-	-	-	-	-	-	-
STAT5A variant (ref. wt)	-	-	-	-	-	-	6.3 (1.2, 33.9)	0.030	-	-	-	-
BCOR variant (ref. wt)	-	-	-	-	-	-	-	-	-	-	-	-
KMT2D variant (ref. wt)	#	#	#	#	#	#	-	-	-	-	-	-
PHF6 variant (ref. wt)	-	-	-	-	-	-	-	-	-	-	-	-
RAD21 variant (ref. wt)	-	-	-	-	-	-	/	/	/	/	/	/
SETBP1 variant (ref. wt)	-	-	-	-	-	-	-	-	-	-	-	-

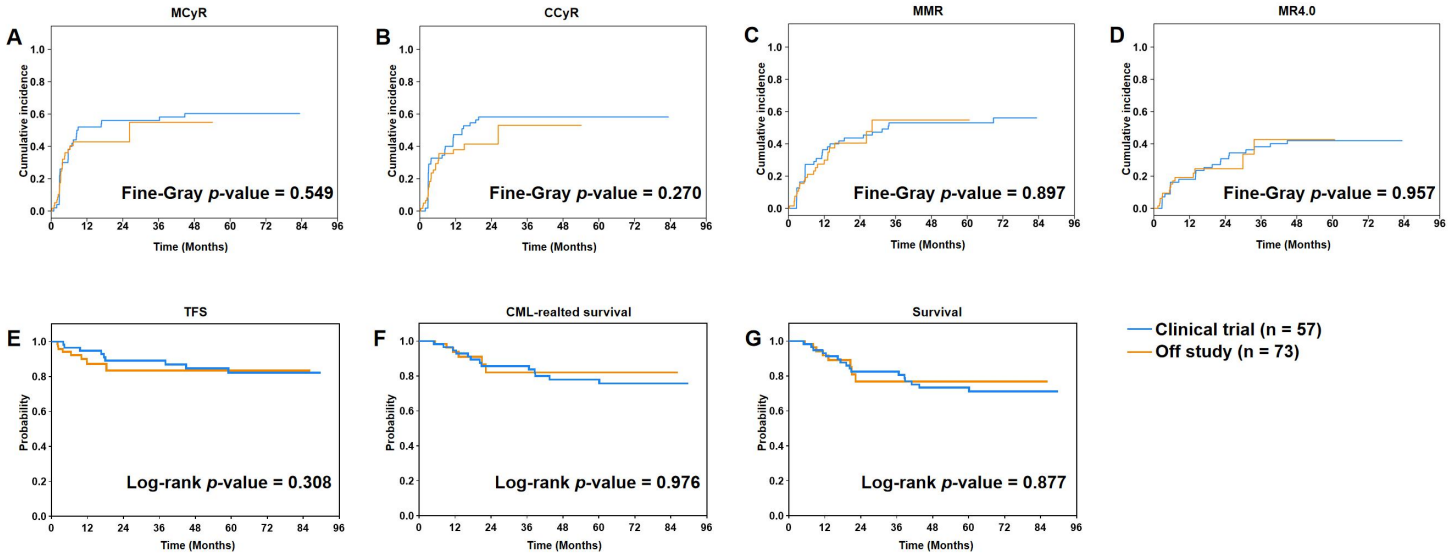
ACAs, additional cytogenetic abnormalities; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CI, confidence interval; HR, hazard ratio; MCyR, major cytogenetic response; mo, months; MMR, major molecular response; MR4.0, molecular response 4.0; QOD, every other day; TFS, transformation-free survival; TKI, tyrosine kinase inhibitor.

*For CCyR, MMR, or MR4, best prior TKI-therapy responses ≥ CCyR *versus* < CCyR; for TFS, CML-realted survival, or survival, best prior TKI-therapy responses ≥ CHR *versus* < CHR.

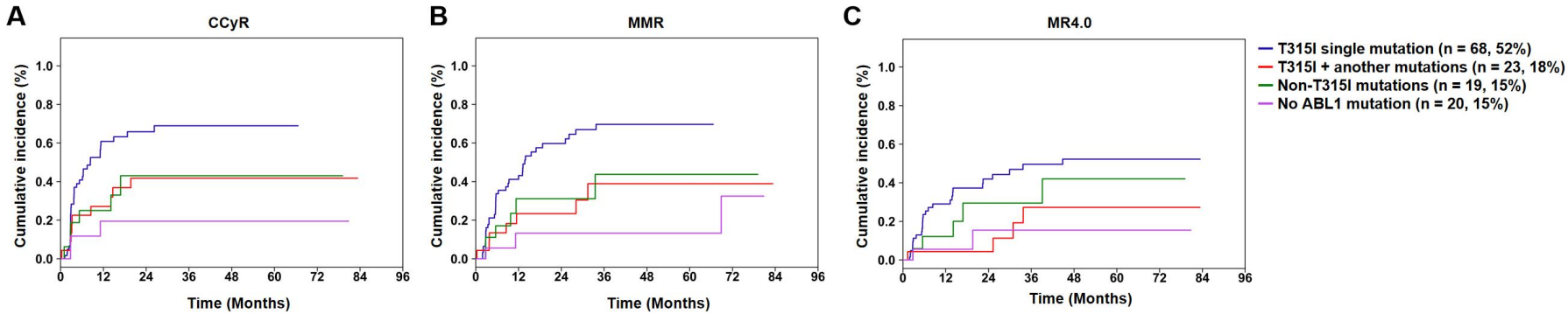
#All subjects harboring *RUNX1* or *KMT2D* variant did not achieve CCyR, MMR or MR4.0.

The '/' denotes that none of the patients harboring the variant experienced the outcome event.

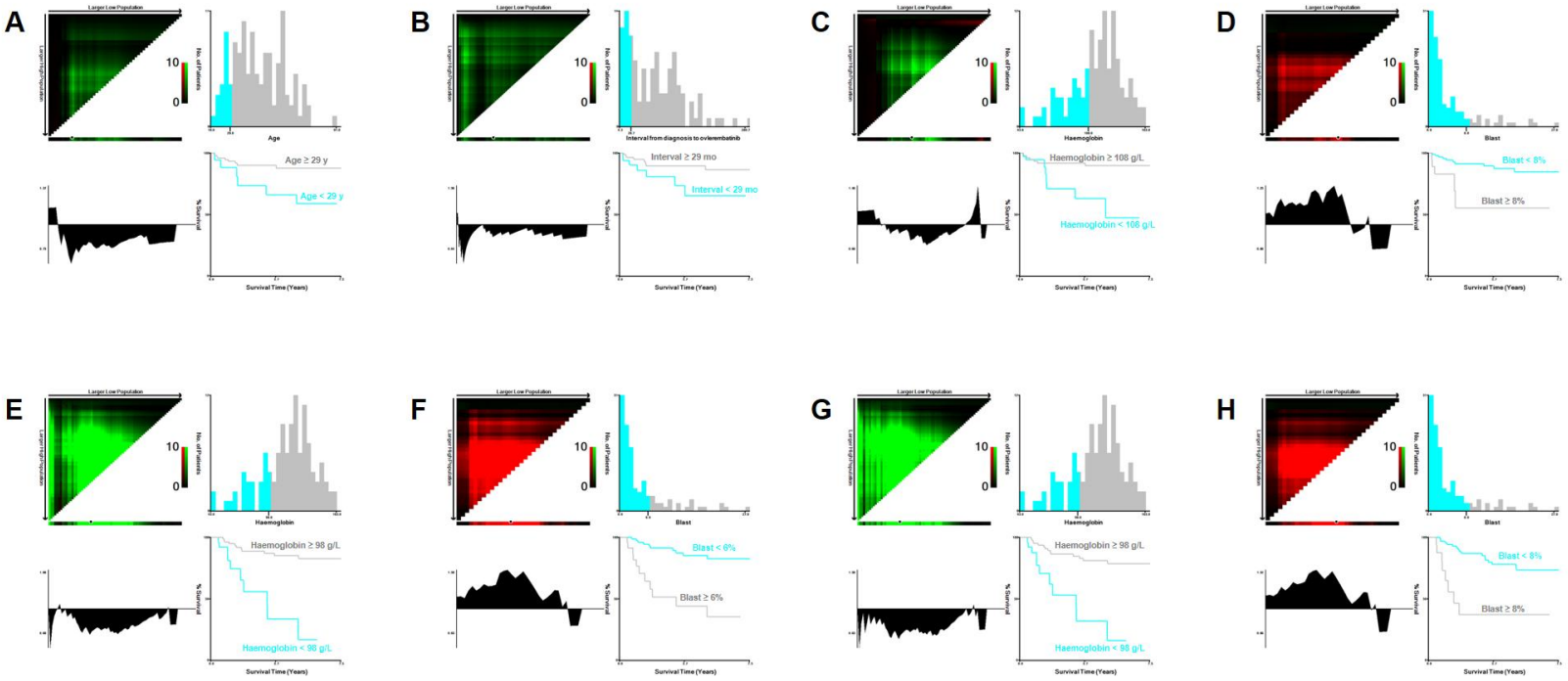
Co-variates listed without corresponding values were included in the initial multi-variable Cox model but excluded during the final stepwise selection; therefore, hazard ratios and *p*-values are not reported for them.



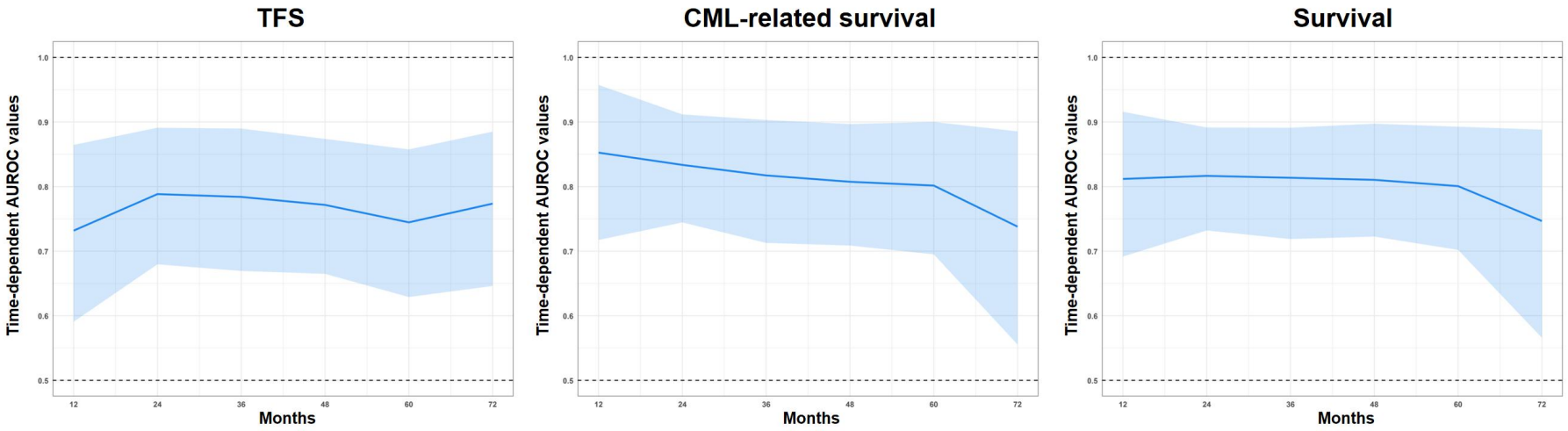
Supplement Figure 1. Comparison of therapy responses and outcomes between the clinical trial cohort and off-study cohort. (**A-D**) Therapy responses; (**E-G**) Outcomes. MCyR, major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; MR4.0, molecular response 4.0; TFS, transformation-free survival.



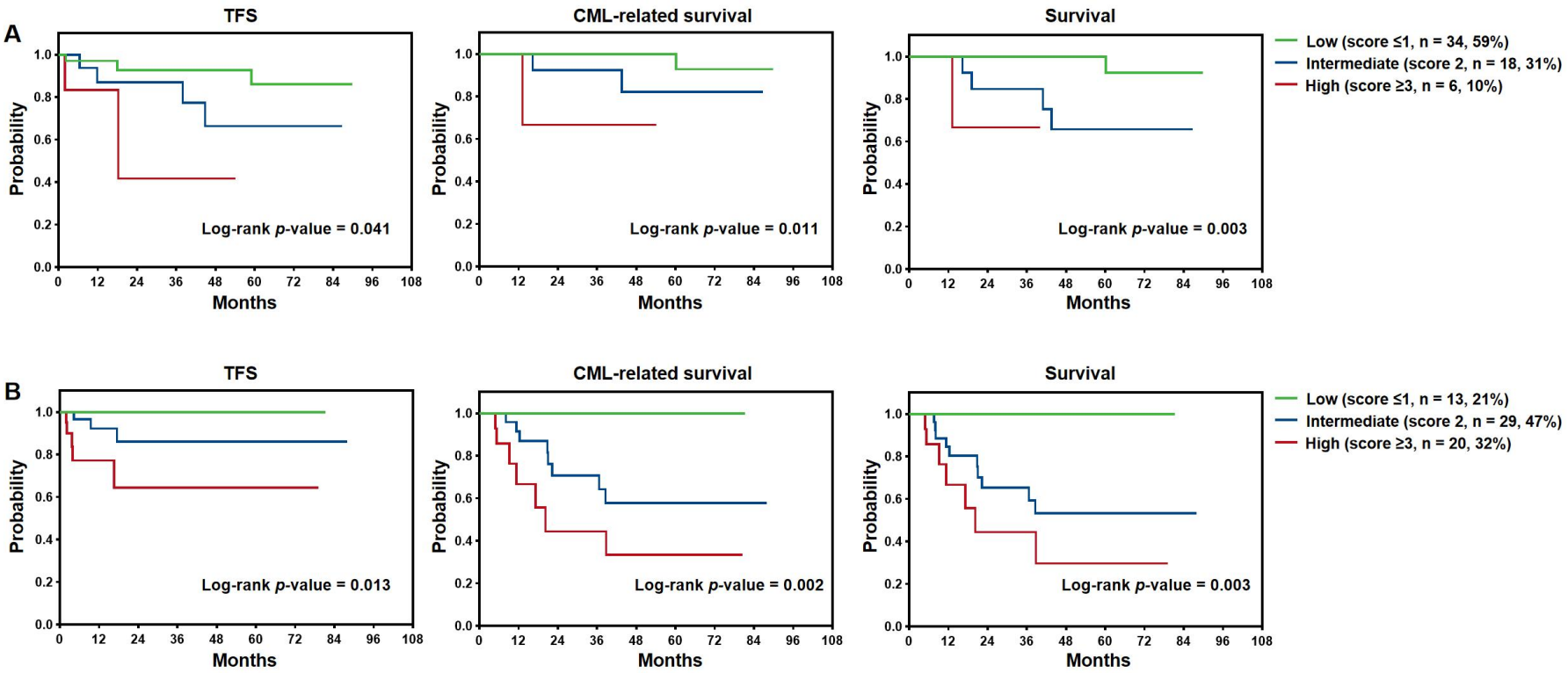
Supplement Figure 2. Responses of olverembatinib by baseline *BCR::ABL1* mutation status in subjects with accelerated phase CML failing prior TKI. (**A**) CCyR, complete cytogenetic response; (**B**) MMR, major molecular response; (**C**) MR4.0, molecular response 4.0.



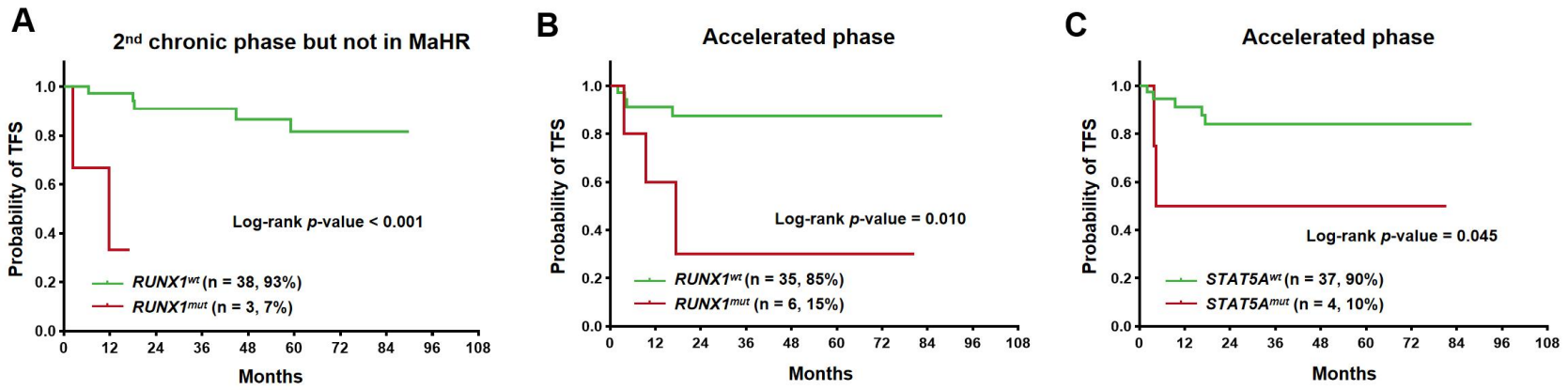
Supplement Figure 3. X-tile analyses to determine the optimal cut-off values of outcomes for continuous co-variates in survival analyses. **(A-D)** For transformation-free survival; **(E-F)** For CML-related survival; **(G-H)** For survival.



Supplement Figure 4. Time-dependent AUROC of the prognostic group for TFS, CML-related survival and survival. AUROC: The area under the receiver-operator characteristic curve; TFS, transformation-free survival.



Supplement Figure 5. Kaplan-Meier curves of TFS, CML-related survival, and survival by the risk prognostic group. (A) 2nd chronic phase but not in MaHR cohorts; (B) Accelerated phase. MaHR, major haematological response; TFS, transformation-free survival.



Supplement Figure 6. Impact of variants on TFS. (A) *RUNX1* variant in the 2nd chronic phase but not in MaHR cohort. (B) *RUNX1* variant in the accelerated phase cohort. (C) *STAT5A* variant in the accelerated phase cohort. MaHR, major haematological response; TFS, transformation-free survival.