haematologica
Journal of the Ferrata Storti Foundation

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Received: May 15, 2025.
Accepted: October 3, 2025.

Citation: Mengyao Yuan, Li Zhou, Weiming Li, Xin Du, Jianyu Weng, Linhua Yang, Yanping Ma, Bingcheng Liu, Zhenfang Liu, Qin Wen, Shasha Zhao, Yanli Zhang, Qingxian Bai, Xianqi Feng, Yanqiu Han, Chunshui Liu, Li Meng, Baohong Wang, Xuehong Ran, Xiaodong Wang, Haiguo Zhang, Yun Zeng, Qing Leng, Lu Yu, Zongru Li, Robert Peter Gale, Xiaojun Huang and Qian Jiang. Olverembatinib in accelerated-phase chronic myeloid leukemia: efficacy and safety evaluation.
Haematologica. 2025 Oct 16. doi: 10.3324/haematol.2025.288249 [Epub ahead of print]

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

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Data-sharing statement Data are available from the corresponding author upon reasonable request compliant with the laws of China.

Acknowledgments We thank medical staff and patients' participants. RPG acknowledges support from the UK National Institute of Health Research (NIHR). QJ acknowledges support from the National Natural Science

Foundation of China (No. 81970140 and No. 82370161).

Funding Funded, in part, by the National Natural Science Foundation of China (No. 81970140 and No. 82370161) to QJ.

Disclosure RPG is a consultant to Antengene Biotech LLC; Consultant Shenzen TargetRx; Medical Director, FFF Enterprises Inc.; a speaker for Janssen Pharma, BeiGene and Hengrui Pharma; Board of Directors: Russian Foundation for Cancer Research Support and Scientific Advisory Board, StemRad Ltd.

Contributions QJ designed the study. QJ, MY, LZ and WL analyzed the data and prepared the typescript. RPG provided valuable insights on data analyses and assisted in preparing the typescript. QJ, LZ, WL, XD, JW, LinY, YM, BL, ZhenL, QW, SZ, YanZ, QB, XF, YH, CL, LM, BW, XR, XW, HZ, YunZ, QL, LuY, ZongL and XH treated the subjects, collected the data and revised the typescript. All the authors approved the final typescript, take responsibility for the content and agreed to it for publication.

Abstract

We studied 130 consecutive subjects who presented with (n = 29) or transformed to (n = 101) accelerated phase chronic myeloid leukemia (CML) and who received olverembatinib. 62 were in 2nd chronic phase. All failed ≥ 1 tyrosine kinase-inhibitors (TKIs) and 91 had *BCR::ABL1*^{T315I}. Median follow-up was 28 months (InterQuartile Range, 10-74 months). The 6-year cumulative incidences of major cytogenetic response (MCyR), complete cytogenetic response (CCyR), major molecular response (MMR) and molecular response 4.0 (MR4.0) were 59% (95% Confidence Interval [CI] (49, 69%), 53% (42, 62%), 52% (41, 62%) and 42% (31, 53%), respectively. The 6-year probabilities of transformation-free survival (TFS), CML-related survival and survival were 81% (72, 90%), 76% (67, 87%) and 71% (61, 82%), respectively. In multi-variable analyses, an interval from diagnosis of CML to olverembatinib start < 29 months, failure to achieve complete hematologic response (CHR) on prior TKI therapy, hemoglobin concentration < 98 g/L, blood and/or bone marrow blasts ≥ 8%, and/or high-risk additional chromosome abnormalities at the start of olverembatinib therapy, as well as not achieving early MCyR on olverembatinib correlated with worse outcomes. *RUNX1* and *STAT5A* variants were significantly associated with worse TFS in the 82 subjects with targeted DNA sequencing data. There were acceptable treatment-related adverse events. We conclude olverembatinib is effective and tolerable in subjects in accelerated phase CML failing prior TKI therapy.

Keywords Chronic myeloid leukemia, accelerated phase, olverembatinib

Introduction

People with accelerated phase chronic myeloid leukemia (CML), *de novo* or after transformation from chronic phase have a poorer prognosis than those with chronic phase CML, especially if previously treated with a 2nd or 3rd-generation tyrosine kinase-inhibitors (2G- or 3G-TKIs).[1–7] Olverembatinib (HQP-1351) is a novel 3G-TKI that acts as an adenosine triphosphate (ATP)-binding site inhibitor targeting both wild-type *BCR:ABL1* kinase and a broad spectrum of *BCR::ABL1* mutants including *T315I.*[8,9] Olverembatinib's *BCR:ABL1* inhibitory activity underlies its clinical utility for CML treatment,[10,11] and its safety and efficacy have been shown in people with extensively treated chronic phase and accelerated phase CML.[12,13] However, there are few recent large studies on therapy of accelerated phase CML, especially in people failing prior TKI therapy. Therefore, we interrogated data from 130 consecutive subjects with accelerated phase CML failing prior TKI-therapy and/or with *BCR::ABL1*^{T315I} receiving olverembatinib. We evaluated efficacy and safety and studied co-variates correlated with outcomes.

Methods

We reviewed medical records of 130 subjects with accelerated phase of CML receiving olverembatinib from June, 2017 to October, 2024 at 20 Chinese centers. The inclusion criteria were as follows: (1) CML subjects in accelerated phase or 2nd chronic phase but not in major haematologic response (MaHR); (2) failure of ≥ 1 prior TKI-therapies (including *T315I* mutation); (3) no prior history of blast phase. Fifty-seven subjects were enrolled in Phase-1/-2 trial of olverembatinib.[12] Co-variates including sex, age, co-morbidities, prior TKIs and therapy response, complete blood count parameters and percentages of blood blasts and basophils at the start of olverembatinib, dose, therapy response and therapy-related adverse events

(TRAEs) during olverembatinib therapy were collected. Co-morbidity(ies) were classified using the Charlson Comorbidity Index.[14,15] Dose adjustments were based on responses and/or TRAEs, guided by clinical protocols for clinical trial cohorts and ELN recommendations for off-study cohorts.[12,16,17] The study was approved by the Ethics Committee of Peking University People's Hospital (2024PHB336-001) and subjects gave written informed consent consistent with the precepts of the Declaration of Helsinki.

Diagnosis and monitoring were done using ELN recommendations.[16,17] Criteria for accelerated phase include ≥ 1 of the following: (1) blood or bone marrow blasts ≥ 15% but < 30%; (2) blood or bone marrow blasts and promyelocytes ≥ 30% with blasts < 30%; (3) blood basophils ≥ 20%; (4) platelet concentration < 100 × 10E + 9/L unrelated to therapy; (5) additional chromosome abnormalities (ACAs) in Ph-chromosome-positive cells, major route on treatment.[16,17] MaHR was defined as complete hematologic response (CHR) or no evidence of leukemia.[12,18] High-risk ACAs included +8, a 2nd Ph-chromosome(+Ph), i(17q), +19, -7/7q-, 11q23, 3q26.2 aberrations and/or complex aberrant cytogenetics.[17] Definition of cytogenetic and molecular responses was based on the ELN recommendations.[16,17]

TRAEs were assessed continuously, graded and reported according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Probable causality was assessed for all TRAEs.

Targeted DNA sequencing

Targeted DNA sequencing was done on 82 subjects from Peking University People's Hospital using the Illumina platform (Illumina, San Diego, CA, USA) with an average coverage depth of 1200-2000x for targeted DNA sequencing (**Supplement Methods**). Candidate genes in the targeted sequencing

panels are displayed in **Supplement Table1**.

Statistics

Pearson chi-squared test was used to analyze categorical covariates. Student's *t*- (normal distribution) or Mann-Whitney U (non-normal distribution) tests were used to analyze continuous covariates. Cumulative incidences of therapy response were calculated using the Fine-Gray test considering competing events defined as olverembatinib withdrawal for any reason, transplant or death. Transformation was defined as blood or bone marrow blasts ≥ 30%. Transformation-free survival (TFS) was calculated from start of olverembatinib therapy to transformation or censored at transplant, death, or last follow-up. Survival was calculated from the start of olverembatinib therapy to death from any cause or censored at transplant or last follow-up. Death after progression was scored as death from CML. Outcomes were calculated by the Kaplan-Meier method and compared by the log-rank test.

Cox regression models were used to identify covariates associated with outcomes. X-tile plots identified optimal cutoffs for continuous covariates in outcomes prediction by standard statistical tests including the log-rank test for survival and means tests, with integrated visualization of statistically validated divisions.[19] Subjects were classified into risk cohorts by significant covariates for assessing outcomes. An internal process with 1000 bootstrap resamples was done to internally validate the predictive group. Time-dependent area under the receiver-operator characteristic curves (AUROC) were used to estimate prediction accuracy.[20]

A two-sided $p < 0.05$ was considered significant. SPSS 26.0 (SPSS, Chicago, IL, USA), R version 4.4.1 (R Core Team, Vienna, Austria) and GraphPad Prism 9 (GraphPad Software Inc., La Jolla, CA, USA) were used for analysis and graphing.

Results

Subjects

130 subjects were studied. The last follow-up was March 2, 2025. The median follow-up was 28 months (IQR, 10-74 months). Baseline covariates are displayed in **Table 1**. Ninety-three (72%) subjects were male. The median age at diagnosis of CML and at the start of olverembatinib therapy were 37 years (InterQuartile Range [IQR], 26-50 years) and 43 years (IQR, 34-57 years), respectively. For 29 subjects (22%), the initial CML diagnosis was accelerated phase, while 101 subjects (78%) in accelerated phase had transformed from chronic phase on TKI therapy. At the olverembatinib start, 68 (51%) subjects were in accelerated phase and 62 (49%) subjects were in 2nd chronic phase but not in MaHR with a history of accelerated phase. The median interval from CML diagnosis to olverembatinib start was 72 months (IQR, 25-121 months). 61 (47%) subjects received two prior TKIs and 48 (37%), ≥ three prior TKIs. One hundred twenty-five subjects (96%) had *e13a2* and/or *e14a2 BCR::ABL1* transcripts and 5 (4%), uncommon transcripts. Sixty-eight (52%) had *BCR::ABL1*^{T315I}; 23 (18%), *BCR::ABL1*^{T315I} and another *ABL1* mutation; 19 (15%), a non-*T315I* mutation; and 20 (15%), no *ABL1* mutation.

Responses and outcomes

Olverembatinib was given every other day. Six (5%) subjects started at 20 mg; 31 (24%), 30 mg; 84 (65%), 40 mg and 9 (7%), 50 mg. One hundred five (81%) subjects achieved an MaHR at a median of 2 month (IQR, 1-5 months) and 94 (72%) subjects achieved a CHR at a median of 3 months (IQR, 2-5 months). Sixty-nine (53%) subjects achieved a major cytogenetic response (MCyR) at a median of 3 months (IQR, 3-6 months); and 61 (47%) achieved a

complete cytogenetic response (CCyR) at a median of 4 months (IQR, 3-9 months). Fifty-six (43%) subjects achieved a major molecular response (MMR); and 40 (31%) achieved a molecular response 4.0 (MR4.0). The 6-year cumulative incidences of MCyR, CCyR, MMR, and MR4.0 were 59% (95% Confidence Interval [CI], [49, 69%]), 53% (42, 62%), 52% (41, 62%), and 42% (31, 53%; **Figure 1A**), respectively. During the follow-up period, eight subjects lost CCyR and six lost MMR. The median durations of CCyR and MMR were 45 months (IQR, 11-69 months) and 46 months (IQR, 14-71 months), respectively. Seventeen (13%) subjects transformed to blast phase. Twenty-four (18%) subjects died from leukemia progression (n = 19), cardio- and cerebro-vascular events (CVEs) (n = 2), COVID-19 (n = 1) or an unknown cause (n = 2). The 6-year probabilities of TFS, CML-related survival and survival were 81% (72, 90%), 76% (67, 87%) and 71% (61, 82%; **Figure 1B**), respectively. Treatment responses and outcomes were similar between the clinical trial and the off-study cohorts (**Supplement Figure 1**).

At the last follow-up, seventy-nine (61%) subjects remained on olverembatinib at doses of 10 mg (n = 1), 20 mg (n = 9), 30 mg (n = 37), 40 mg (n = 31) and 50 mg (n = 1); of these, 43 (54%) remained on their olverembatinib starting dose. Ten (8%) subjects switched to imatinib (n = 1), flumatinib (n = 2) or TGRX-678 (n = 7) because of therapy failure (n = 7), TRAEs (n = 1), cost (n = 1) or subject and/or physician choice (n = 1). Two (2%) subjects discontinued olverembatinib therapy; one because of an arterial obstruction and the other because of an intra-cerebral hemorrhage. Fourteen (11%) subjects received a transplant.

Co-variates associated with responses and outcomes

Results of univariable analyses are displayed in **Supplement Table 2**. There were no interactions between covariates. In multivariable analyses

comorbidity (p = 0.018 - 0.049), a longer interval from diagnosis of CML to olverembatinib therapy (p < 0.001 - 0.002), best therapy response on prior TKI therapy < CCyR (p < 0.001), lower hemoglobin concentration at the start of olverembatinib (p = 0.008), and harboring other *ABL1* mutations or no *ABL1* mutation by Sanger sequencing (vs. a single *T315I* mutation; p = 0.003 - 0.027) were significantly associated with lower cumulative incidences of CCyR, MMR and/or MR4.0 (**Table2**; **Supplement Figure 2**). Additionally, a briefer interval from diagnosis of CML to olverembatinib therapy (p < 0.001), best therapy response on prior TKI therapy < CHR (p = 0.004 - 0.037), lower hemoglobin concentration (p < 0.001), higher blood or bone marrow blasts (p = 0.017), high-risk ACAs (p = 0.026 - 0.042) at start of olverembatinib, and no MCyR at 3 months after olverembatinib start (p = 0.006) were significantly associated with worse TFS, CML-related survival and/or survival (**Table 2**). There were no statistically significant differences in treatment response and outcomes between subjects in the accelerated phase and those in 2nd chronic phase but not in MaHR with a history of accelerated phase at the olverembatinib start.

Optimal cutoff values for continuous covariates in survival analyses of therapy outcomes are shown in **Supplement Figure 3**. The cutoff values were defined as 29 months for the interval from diagnosis of CML to olverembatinib start, 98 g/L for hemoglobin concentration, and 8% for blood and/or bone marrow blasts. In multivariable analyses, an interval from diagnosis of CML to olverembatinib start < 29 months (p = 0.001), best therapy response on prior TKI therapy < CHR (p = 0.003 - 0.030), hemoglobin concentration < 98 g/L (p < 0.001), blood and/or bone marrow blasts ≥ 8% (p = 0.003 - 0.011), and/or high-risk ACAs (p = 0.040 - 0.042) at the start of olverembatinib therapy, and/or no MCyR at 3 months after olverembatinib start (p = 0.012) were significantly associated with worse TFS, CML-related survival and/or survival (**Table 3**).

We used these prognostic covariates for outcomes with each scored as 1 point,

to divide the 120 subjects with complete datasets into 3 risk prognostic cohorts: (1) low- (score ≤ 1; n = 47, 39%); (2) intermediate- (score 2; n = 47, 39%) and high-risk (score ≥ 3; n = 26, 22%). The corresponding 6-year probabilities of TFS were 89% (78%, 100%), 77% (63%, 95%) and 59% (36%, 80%; p = 0.004), respectively; CML-related survival, 94% (84%, 100%), 67% (52%, 87%) and 38% (18%, 72%; $p < 0.001$), respectively and survival, 94% (83%, 100%), 58% (43%, 78%) and 36% (16%, 69%; $p < 0.001$; **Figures 2 A** to **C**), respectively. Time-dependent AUROCs of the risk prognostic group for TFS, CML-related survival or survival showed good prediction sensitivity and specificity with 1-, 2-, 3-, 4-, 5- and 6-year AUROCs of 0.73 - 0.85 (**Figures 2 D** to **F; Supplement Figure 4**).

We evaluated the outcomes by the risk prognostic group in the accelerated phase and 2nd chronic phase but not in MaHR cohorts, respectively. There were significant differences in TFS, CML-related survival and survival by the risk prognostic group in both cohorts (p = 0.002 - 0.041; **Supplement Figure 5**).

Genomics and cytogenetics

In the 82 subjects with targeted DNA sequencing data, 72 (88%) had non-*ABL1* somatic variants with a median of 2 (IQR, 1-3). The most frequent variants were *ASXL1* (n = 58), *KMT2C* and *RUNX1* (n = 9 each), *DNMT3A*, *IKZF1* and *STAT5A* (n = 5 each) and *BCOR*, *KMT2D*, *RAD21*, *PHF6* and *SETBP1* (n = 4 each; **Figure 3 A**). Twenty-five of 58 subjects with an *ASXL1* variant had $ASXL1^{G646Wfs*12}$.

In pairwise analyses of genomics and/or cytogenetics, there was a significant co-occurrence of $ASXL1^{non\text{-}G646Wfs*12}$ and *SETBP1* variants (n = 4; p = 0.030), *RUNX1* and *IKZF1* variants (n = 3; p = 0.008) and *ABCB1* and *GNAS* variants

(n = 2; *p* = 0.003; **Figure 3 B**).

Somatic variants with a frequency ≥ 5% and clinical covariates were analyzed to explore prognostic correlations. All subjects harboring *RUNX1* or *KMT2D* variants did not achieve CCyR, MMR or MR4.0 (**Figure 4 A-F**). In multivariable analyses *RUNX1* variants (Hazard Ratio [HR] = 9.4 [2.7, 33.2]; *p* < 0.001) and *STAT5A* variants (HR = 6.3 [1.2, 33.9]; *p* = 0.030) were significantly-associated with worse TFS but not CML-related survival or survival (**Figure 4 G and H**; **Supplement Table 3**). Other variants like *ASXL1*, *ABL1* and co-occurrence of *ASXL1*$^{non\text{-}G646Wfs*12}$ and *SETBP1* variants were not significantly correlated with responses and outcomes.

RUNX1 and *STAT5A* variants remained significantly associated with worse TFS in the accelerated phase cohort; *RUNX1* variant was also significantly associated with worse TFS in 2nd chronic phase but not in MaHR cohort (**Supplement Figure 6**). The impact of the *STAT5A* variant on outcomes was not assessed in the 2nd chronic phase but not in MaHR cohort because only one subject harbored *STAT5A* variant.

Safety

Fifty-two (42%) subjects developed a ≥ grade-3 hematological TRAE including thrombocytopenia (n = 50, 40%), leukopenia (n = 19, 15%) and neutropenia (n = 15, 12%; **Table 4**). The most frequent non-hematologic (any grade) TRAE was skin hyper pigmentation (n = 65, 53%), followed by hypertriglyceridemia (n = 46, 38%), proteinuria and hypocalcemia (n = 39, 32% each; **Table 4**). CVEs were observed in 32 (27%) subjects including hypertension (n = 16), arterial and/or venous thromboses (n = 6), pericardial effusion (n = 5), sinus tachycardia (n = 4), atrial fibrillation and pulmonary arterial hypertension (n = 2 each), congestive heart failure and sinus bradycardia (n = 1 each).

Discussion

Olverembatinib was effective and tolerable in patients with accelerated phase CML failing prior TKI therapy. TRAEs were modest and similar to those in subjects in chronic phase receiving olverembatinib.[13] We also identified clinical and laboratory covariates correlated with therapy responses and outcomes.

The treatment of accelerated phase CML is challenging. In particular, outcomes of transformed accelerated phase CML are suboptimal, even when 2G-TKIs and ponatinib are used.[2–6] Our data show that olverembatinib may be a preferable therapeutic option. In addition, we found that the intermediate and high-risk cohorts identified based on the adverse adverse prognostic factors had poor outcomes on olverembatinib treatment. These patients should consider more potent therapeutic strategies, such as combination therapy with a novel agent or transplantation.

Olverembatinib was designed to be highly active against *BCR::ABL1*^{T315I} mutants.[8,12] A prior study reported a higher response rate to olverembatinib in subjects with *BCR::ABL1*^{T315I} compared with controls.[12] We observed significant differences in CCyR, MMR, and MR4.0 but not in TFS, CML-related survival, and survival between subjects with and without *BCR::ABL1*^{T315I}. Perhaps this is because other cytogenetic variants besides *ABL1* variants trigger the accelerated phase or disease progression on TKI therapy.

It is well known that additional cytogenetic and genetic abnormalities confer CML resistance to TKI and drive leukemia transformation.[21] *RUNX1*, the most frequently mutated gene in CML blast phase, has been implicated in CML transformation, as demonstrated across several studies.[22–27] The

constitutively activated *JAK2/STAT5* pathway triggers *BCR::ABL1*-based CML pathogenesis and is also relevant to acquired TKI resistance.[28–30] Our study identified that subjects with accelerated phase CML failing prior TKI therapy harboring *RUNX1* or *STAT5A* variants were at a higher risk of disease transformation on olverembatinib therapy compared to those without these variants. We recommend that they should consider more effective therapy.

ASXL1 variants in chronic phase CML were reported to be associated with worse failure-free survival in imatinib- or nilotinib- treated newly diagnosed patients.[31,32] We did not find a negative impact of the *ASXL1* variant on TFS, CML-related survival, and survival in those with TKI failure accelerated phase CML receiving olverembatinib therapy.

The occurrence of CVEs is a critical safety concern during 3G-TKI treatment. In this study, the incidence of CVEs was 27% with the most common being hypertension (13%) and arterial and/or venous obstructive events (5%), which were comparable to those reported in the chronic phase population treated with olverembatinib.[12,13] However, the rates were lower than those reported for ponatinib, which were 26% for hypertension and >10% for arterial and/or venous obstructive events, respectively.[6] The discrepancy may be attributed to our subjects' younger median age (43 versus 60 years). Other potential reasons include the shorter median follow-up period in our study (28 versus 32 months) and the smaller proportion of subjects with hypertension comorbidities before olverembatinib initiation (14% versus 47%). It is imperative that future clinical practice will focus on the surveillance of CVEs in patients during long-term olverembatinib therapy.

Our study has limitations. First, there are relatively few subjects and they are heterogeneous. Second, different starting doses of olverembatinib were given. Third, variant topographies differed. Fourth, some subjects were on

clinical trials, while others were not. Lastly, we could not strictly monitor compliance because of diverse contributing centers.

We conclude olverembatinib is effective and tolerable in subjects in accelerated phase CML failing prior TKI-therapy.

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Table 1. Subject covariates.

Covariates	Total (n = 130)
Age at diagnosis of CML (y), median (IQR)	37 (26, 50)
Age at the start of olverembatinib therapy (y), median (IQR)	43 (34, 57)
Male, n (%)	93 (72%)
Phase at diagnosis, n (%)	
Chronic phase	101 (78%)
Accelerated phase	29 (22%)
BCR::ABL transcript, n (%)	
e13a2 and/or e14a2	125 (96%)
Uncommon transcripts	5 (4%)
Co-morbidity, n (%)	41 (32%)
Interval from diagnosis of CML to olverembatinib therapy (mo), median (IQR)	72 (25, 121)
Number of lines of prior TKI-therapy, n (%)	
1	21 (16%)
2	61 (47%)
≥ 3	48 (37%)
Best therapy response on prior TKI therapy, n (%)	
No CHR	30 (23%)
CHR	63 (48%)
CCyR	10 (8%)
MMR	16 (12%)
MR4.0	6 (5%)
Unknown	5 (4%)
Phase at the start of olverembatinib therapy, n (%)	
2nd chronic phase*	62 (48%)
Accelerated phase	

Blasts 15-29%	5 (4%)
Basophils ≥ 20%	23 (18%)
Major route ACA/Ph+	25 (19%)
Platelet concentration <100 × 10E + 9/L unrelated to therapy	2 (2%)
≥ 2 co-variates	13 (10%)
WBC (× 10E + 9/L), median (range)	7 (2, 300)
hemoglobin (g/L), median (range)	118 (43, 163)
Platelets (× 10E + 9/L), median (range)	186 (12, 2999)
Blood and/or bone marrow blasts (%), median (range)	2 (0, 27)
Basophils (%), median (range)	4 (0, 54)
BCR::ABL1 mutation status by Sanger sequencing, n (%)	
No *ABL1* mutation	20 (15%)
T315I single mutation	68 (52%)
T315I + another mutations	23 (18%)
Non-*T315I* mutations	19 (15%)
ACA Ph+, n (%)	41 (33%)
High-risk, n (%)	27 (21%)
Complex aberrant karyotype, n (%)	19 (15%)
+8, n (%)	15 (12%)
+Ph, n (%)	10 (8%)
i(17q), n (%)	7 (6%)
−7/del(7q), n (%)	5 (4%)

*At olverembatinib initiation, 62 subjects (48%) were in the 2nd chronic phase but not in MaHR.

ACA, additional chromosome abnormalities; CHR, complete hematologic response; CCyR, complete cytogenetic response; IQR, interquartile range; MaHR, major

haematologic response; MMR, major molecular response; MR4.0, molecular response 4.0; mo, month; WBC, white blood cells; y, year.

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

Covariates	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
Comorbidity(ies) (ref. none)	-	-	0.5 (0.2, 1.0)	0.049	0.3 (0.1, 0.8)	0.018	-	-	-	-	-	-
Interval from diagnosis to olverembatinib start, mo (continuous)	0.9 (0.8, 0.9)	<0.001	0.9 (0.8, 1.0)	0.001	0.9 (0.8, 1.0)	0.002	0.8 (0.7, 0.9)	<0.001	-	-	-	-
Best prior TKI-therapy responses*	4.6 (2.4, 8.8)	<0.001	5.1 (2.7, 9.6)	<0.001	9.9 (4.2, 23.2)	<0.001	0.2 (0.1, 0.7)	0.011	0.4 (0.1, 0.9)	0.037	0.3 (0.1, 0.7)	0.004
hemoglobin (g/L)	1.2 (1.0, 1.3)	0.008	-	-	-	-	-	-	0.7 (0.5, 0.8)	<0.001	0.7 (0.6, 0.8)	<0.001
Blood and/or bone marrow blasts (%)	-	-	-	-	-	-	2.7 (1.2, 6.0)	0.017	2.0 (1.0, 4.0)	0.057	2.0 (1.0, 4.1)	0.059
High-risk ACAs (ref. no)	-	-	-	-	-	-	-	-	3.0 (1.0, 8.5)	0.042	2.9 (1.1, 7.4)	0.026
Baseline *BCR::ABL1* mutation status (ref. Single *T315I* mutation)		0.027		0.003		0.009	-	-	-	-	-	-
T315I + another mutations	0.5 (0.2, 1.1)	0.092	0.4 (0.2, 1.0)	0.040	0.3 (0.1, 0.8)	0.022	-	-	-	-	-	-
Non-*T315I* mutations	0.7 (0.3, 1.8)	0.514	0.7 (0.3, 1.7)	0.395	1.2 (0.4, 3.2)	0.751	-	-	-	-	-	-
No mutation	0.2 (0.1, 0.6)	0.006	0.2 (0.1, 0.4)	0.001	0.2 (0.1, 0.5)	0.006	-	-	-	-	-	-
Achieving MCyR within 3 months of olverembatinib (ref. failure)	-	-	-	-	-	-	0.3 (0.1, 0.4)	0.006	-	-	-	-

ACAs, additional cytogenetic abnormalities; CCyR, complete cytogenetic response; CML, chronic myeloid leukeamia; CI, confidence interval; HR, hazard ratio; MCyR, major cytogenetic response; MMR, major molecular response; MR4.0, molecular response 4.0; mo, months; TFS, transformation-free survival

*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.

Table 3. Multi-variable analyses results of outcomes using category variables.

Co-variates using category variables	TFS		CML-related survival		Survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Interval from diagnosis to olverembatinib start < 29 mo (ref. ≥ 29 mo)	6.0 (2.0, 17.8)	0.001	-	-	-	-
Best prior TKI-therapy responses < CHR (ref. ≥ CHR)	3.6 (1.1, 11.2)	0.030	3.0 (1.1, 8.1)	0.026	3.7 (1.6, 8.8)	0.003
hemoglobin < 98 g/L	-	-	7.5 (2.6, 21.6)	<0.001	6.4 (2.5, 16.6)	<0.001
Blood and/or bone marrow blasts ≥ 8%	5.1 (1.7, 15.3)	0.003	4.4 (1.6, 12.4)	0.005	3.7 (1.3, 9.9)	0.011
High-risk ACAs (ref. no)	-	-	3.0 (1.0, 8.4)	0.042	2.8 (1.0, 6.9)	0.040
Failure to achieve MCyR within 3 months (ref. Achieving)	4.7 (2.0, 15.8)	0.012	-	-	-	-

ACAs, additional cytogenetic abnormalities; CHR, complete haematologic response; CML, chronic myeloid leukeamia; CI, confidence interval; HR, hazard ratio; MCyR, major cytogenetic response; mo, months; TFS, transformation-free survival.

Table 4. Treatment-related adverse events (subjects with event / evaluable subjects, %).

Hematologic	**Grade ≥ 3**	**Grade ≥ 4**
Thrombocytopenia	50/124 (40)	37/124 (30)
Leukopenia	19/124 (15)	6/124 (5)
Neutropenia	15/124 (12)	8/124 (6)
Non-hematologic	**Any grades**	**Grade ≥ 2**
Cardio- and cerebro-vascular toxicity	32/120 (27)	21/120 (18)
Hypertension	16/120 (13)	11/120 (9)
Arterial and/or venous obstructive events	6/128 (5)	6/128 (5)
Pericardial effusion	5/128 (4)	5/128 (4)
Sinus tachycardia	4/128 (3)	3/128 (2)
Atrial fibrillation	2/128 (2)	2/128 (2)
Pulmonary arterial hypertension [§]	2/128 (2)	1/128 (1)
Heart failure	1/128 (1)	1/128 (1)
Sinus bradycardia	1/128 (1)	0
Hepatic and renal toxicity	67/122 (55)	21/122 (17)
Proteinuria	39/122 (32)	11/122 (9)
Aspartate aminotransferase increased	35/122 (29)	4/122 (3)
Glutamyl transferase increased	31/122 (25)	6/122 (5)
Alanine aminotransferase increased	30/122 (25)	5/122 (4)
Alkaline phosphatase increased	20/122 (16)	2/122 (2)
Endocrine and metabolic toxicity	69/117 (59)	19/117 (16)
Hypertriglyceridemia	46/120 (38)	7/120 (6)
Hypocalcemia	39/122 (32)	4/122 (3)
Hyperglycemia	29/122 (24)	3/122 (2)
Hypoproteinemia	28/122 (23)	2/122 (2)

Hypokalemia	24/122 (20)	1/122 (1)
Hyponatremia	22/122 (18)	2/122 (2)
Lipase increased	9/117 (8)	4/117 (3)
Thyroid dysfunction *	2/111 (2)	1/111 (1)
Gastrointestinal toxicity	8/118 (7)	2/118 (2)
Nausea and/or vomiting	6/122 (5)	1/122 (1)
Diarrhea	1/119 (1)	1/119 (1)
Pancreatitis	1/121 (1)	0
Others	-	-
Skin pigmentation	65/122 (53)	0
Fever	23/115 (20)	9/115 (8)
Creatine kinase increased	23/121 (19)	8/121 (7)
Muscle and/or joint pain	19/121 (16)	1/121 (1)
Sexual dysfunction [#]	17/109 (16)	1/109 (1)
Rash	18/122 (15)	3/122 (2)
Fatigue	14/122 (11)	2/122 (2)
Pneumonia	7/112 (6)	4/112 (4)
Hemorrhage	3/120 (3)	0

[§] Pulmonary arterial hypertension (PAH) was identified as highly suspected based on echocardiographic (UCG) screening.

* Thyroid dysfunction was characterized by elevated thyroid-stimulating hormone (TSH) levels, with or without reduced free triiodothyronine (FT3) / free thyroxine (FT4) hormone levels in this study.

[#] Sexual dysfunction was assessed through follow-up inquiries and patients self-reports. All reported cases occurred in male patients, presenting primarily as erectile dysfunction and decreased libido.

Figure Legends

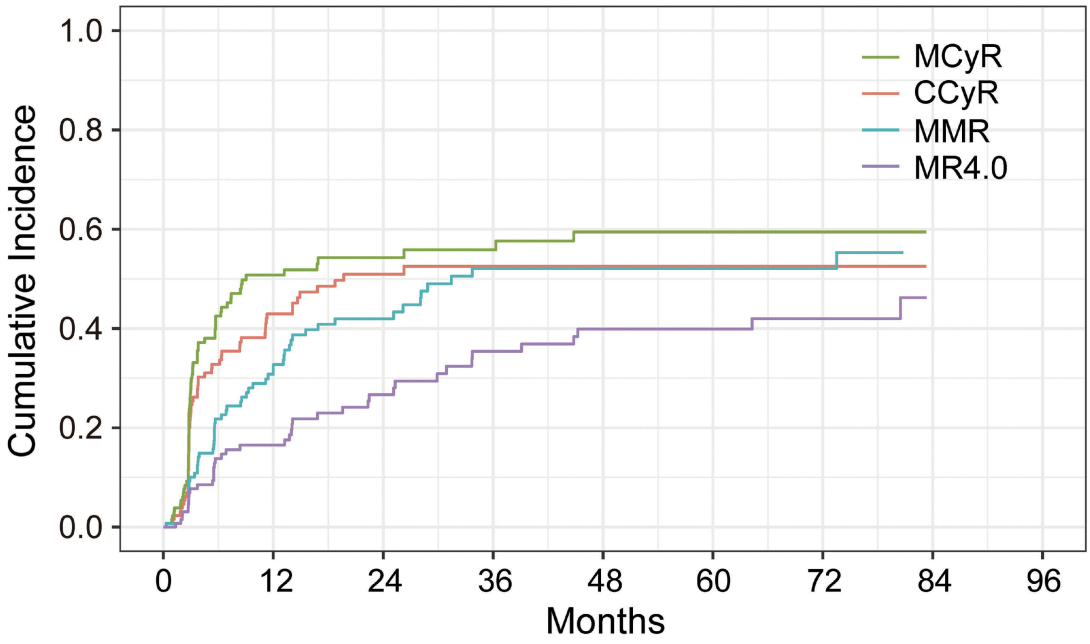
Figure 1. Responses and outcomes. (A) Responses; **(B)** Outcomes. MCyR, major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; MR4.0, molecular response 4.0; TFS, transformation-free survival.

Figure 2. Prognostic value of the risk group by the number of adverse prognostic co-variates. (A-C) Kaplan-Meier curves of transformation-free survival (TFS), CML-related survival, and survival. **(D-F)** ROC curves of the risk group for 1-, 2-, 3-, 4-, 5- and 6-year probabilities of TFS, CML-related survival, and survival.

Figure 3. Variant profiles. (A) Variant distribution; (B) Pair-wise associations between cytogenetics and/or genomics.

Figure 4. Impact of variants on subsequent cytogenetic and molecular response, and TFS. (A-C) *RUNX1* variant on cumulative incidence of CCyR, MMR and MR4.0. **(D-F)** *KMT2D* variant on cumulative incidence of CCyR, MMR and MR4.0. **(G-H)** *RUNX1* and *STAT5A* variant on probability of TFS. CCyR, complete cytogenetic response; MMR, major molecular response; MR4.0, molecular response 4.0; TFS, transformation-free survival

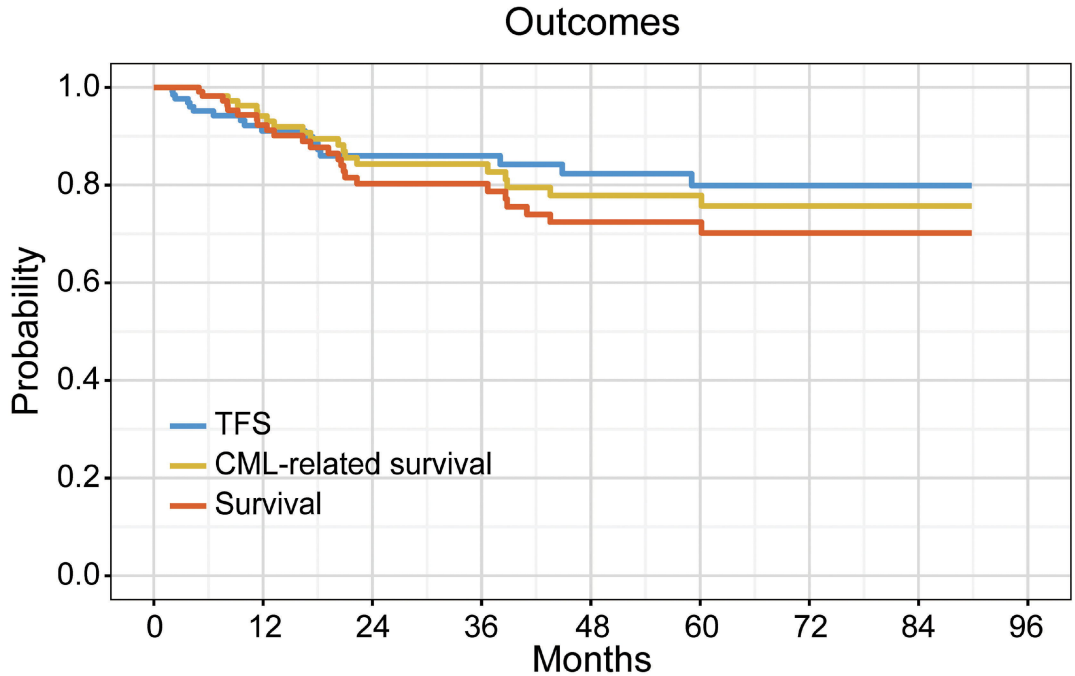
A



Number at risk

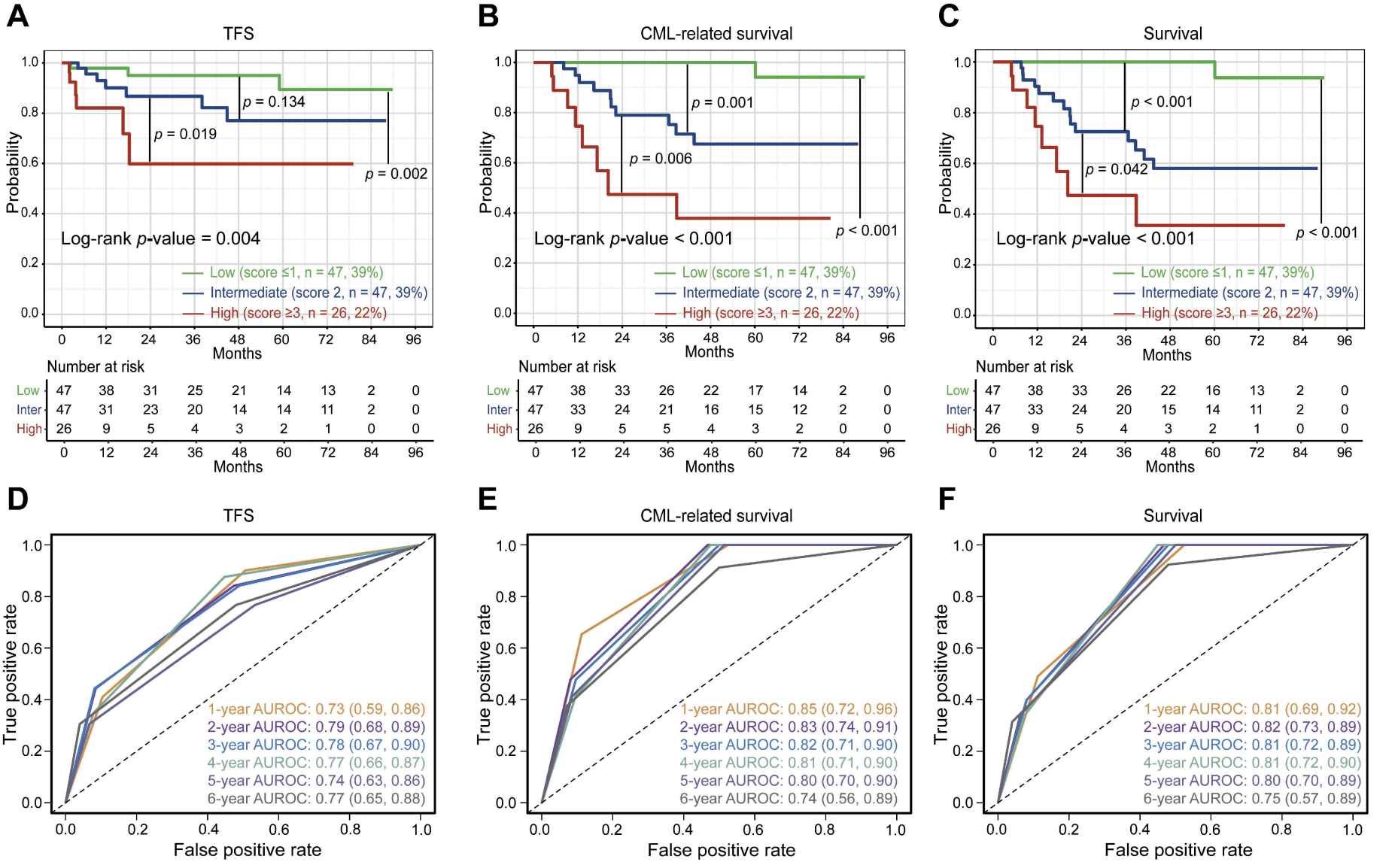
MCyR	130	36	20	13	7	4	3	0	0
CCyR	130	43	21	13	9	5	4	0	0
MMR	130	57	30	16	12	7	5	0	0
MR4.0	130	66	40	26	17	12	9	0	0

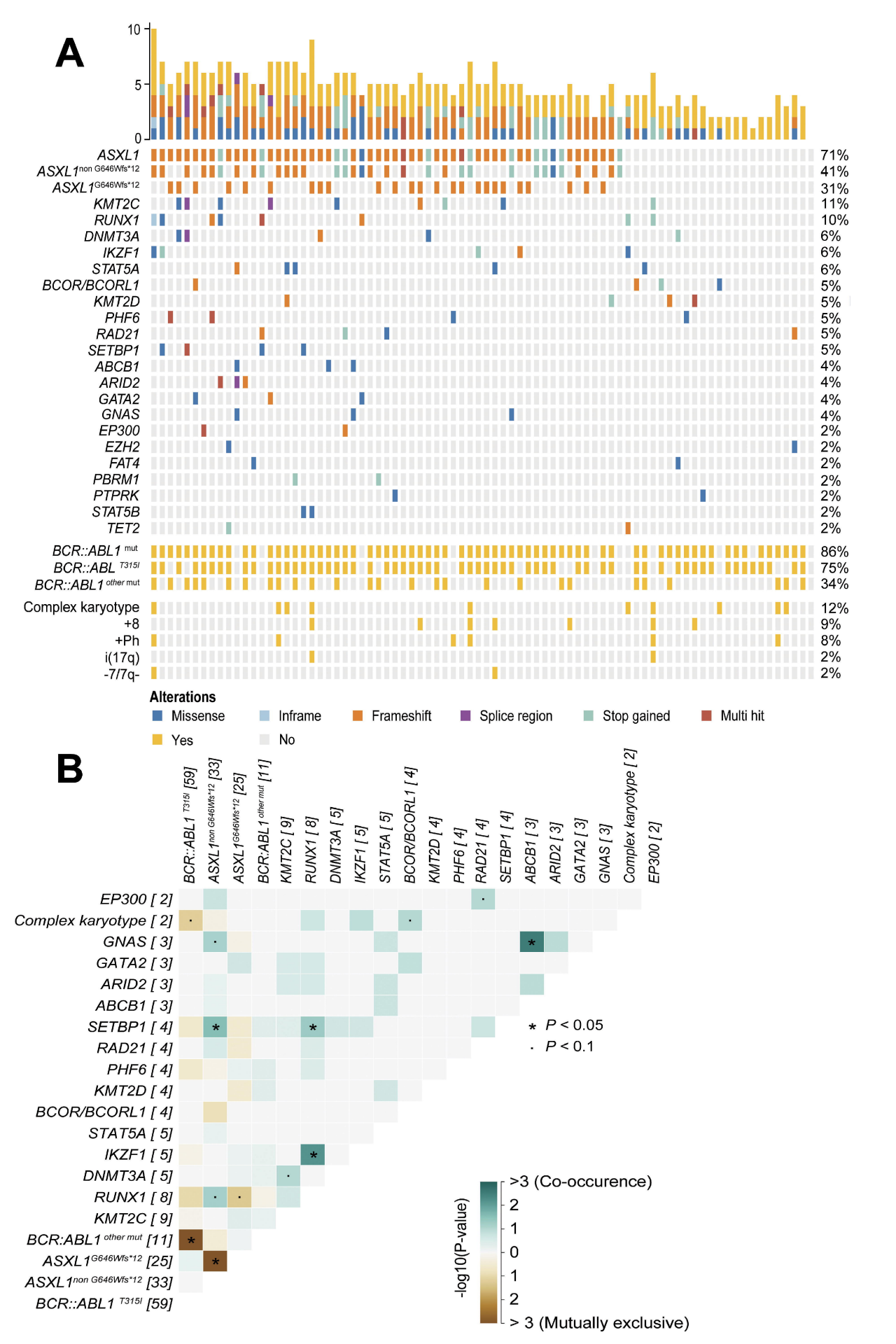
B

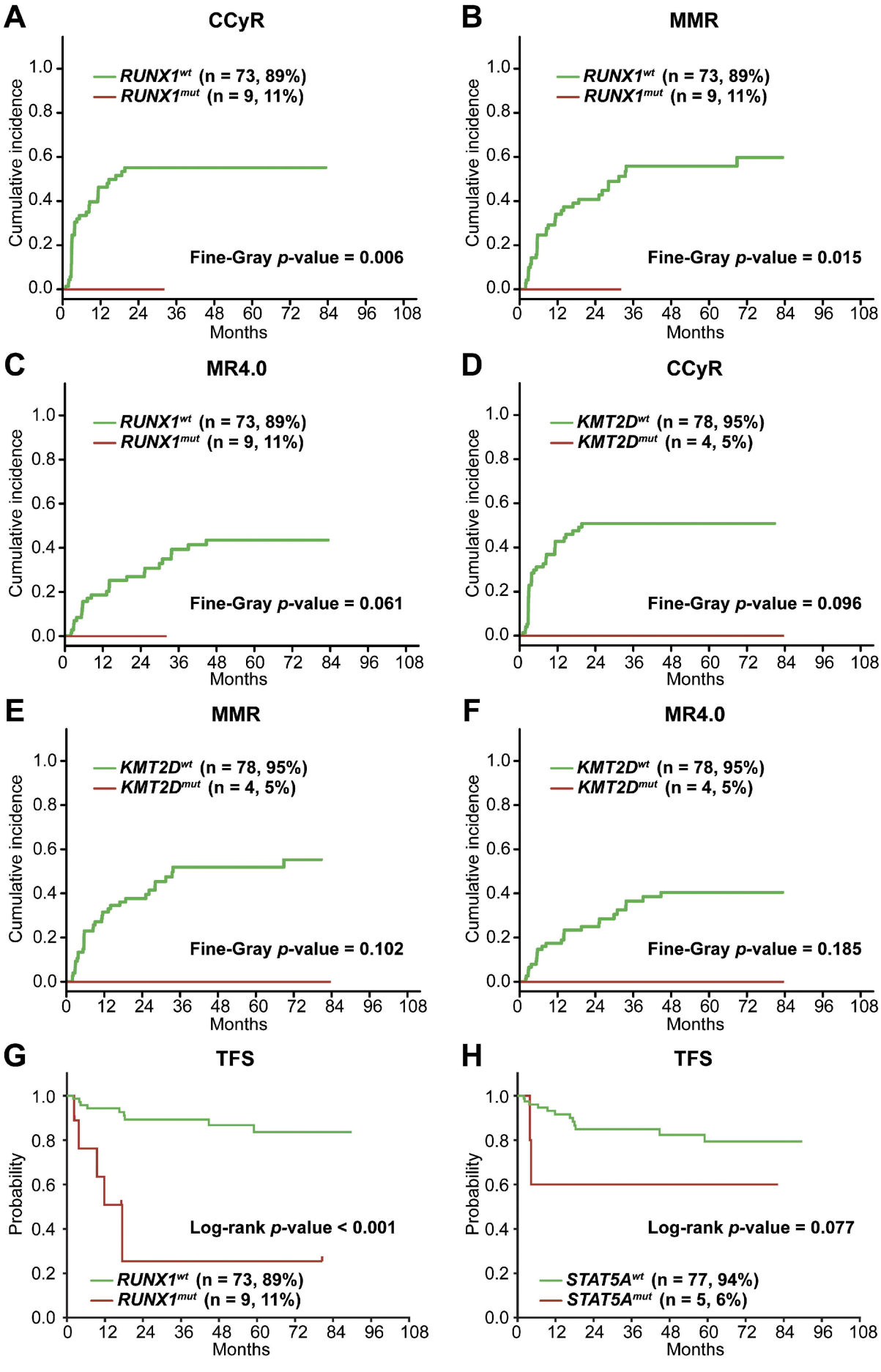


Number at risk

TFS	130	82	61	50	39	31	25	4	0
CML-related survival	130	85	64	53	43	36	28	4	0
Survival	130	85	64	51	41	33	25	4	0


A
TFS
Probability
p = 0.134
p = 0.019
p = 0.002
Log-rank p-value = 0.004
Low (score ≤1, n = 47, 39%)
Intermediate (score 2, n = 47, 39%)
High (score ≥3, n = 26, 22%)
Months
Number at risk
Low 47 38 31 25 21 14 13 2 0
Inter 47 31 23 20 14 14 11 2 0
High 26 9 5 4 3 2 1 0 0
B
CML-related survival
p = 0.001
p = 0.006
p < 0.001
Log-rank p-value < 0.001
Low 47 38 33 26 22 17 14 2 0
Inter 47 33 24 21 16 15 12 2 0
High 26 9 5 5 4 3 2 0 0
C
Survival
p < 0.001
p = 0.042
p < 0.001
Log-rank p-value < 0.001
Low 47 38 33 26 22 16 13 2 0
Inter 47 33 24 20 15 14 11 2 0
High 26 9 5 4 3 2 1 0 0
D
TFS
True positive rate
False positive rate
1-year AUROC: 0.73 (0.59, 0.86)
2-year AUROC: 0.79 (0.68, 0.89)
3-year AUROC: 0.78 (0.67, 0.90)
4-year AUROC: 0.77 (0.66, 0.87)
5-year AUROC: 0.74 (0.63, 0.86)
6-year AUROC: 0.77 (0.65, 0.88)
E
CML-related survival
1-year AUROC: 0.85 (0.72, 0.96)
2-year AUROC: 0.83 (0.74, 0.91)
3-year AUROC: 0.82 (0.71, 0.90)
4-year AUROC: 0.81 (0.71, 0.90)
5-year AUROC: 0.80 (0.70, 0.90)
6-year AUROC: 0.74 (0.56, 0.89)
F
Survival
1-year AUROC: 0.81 (0.69, 0.92)
2-year AUROC: 0.82 (0.73, 0.89)
3-year AUROC: 0.81 (0.72, 0.89)
4-year AUROC: 0.81 (0.72, 0.90)
5-year AUROC: 0.80 (0.70, 0.89)
6-year AUROC: 0.75 (0.57, 0.89)


A
10
5
0
ASXL1 71%
ASXL1non G646Wfs*12 41%
ASXL1G646Wfs*12 31%
KMT2C 11%
RUNX1 10%
DNMT3A 6%
IKZF1 6%
STAT5A 6%
BCOR/BCORL1 5%
KMT2D 5%
PHF6 5%
RAD21 5%
SETBP1 5%
ABCB1 4%
ARID2 4%
GATA2 4%
GNAS 4%
EP300 2%
EZH2 2%
FAT4 2%
PBRM1 2%
PTPRK 2%
STAT5B 2%
TET2 2%
BCR::ABL1 mut 86%
BCR::ABL T315I 75%
BCR::ABL1 other mut 34%
Complex karyotype 12%
+8 9%
+Ph 8%
i(17q) 2%
-7/7q- 2%
Alterations
Missense
Inframe
Frameshift
Splice region
Stop gained
Multi hit
Yes
No
B
BCR::ABL1 T315I [59]
ASXL1non G646Wfs*12 [33]
ASXL1G646Wfs*12 [25]
BCR:ABL1 other mut [11]
KMT2C [9]
RUNX1 [8]
DNMT3A [5]
IKZF1 [5]
STAT5A [5]
BCOR/BCORL1 [4]
KMT2D [4]
PHF6 [4]
RAD21 [4]
SETBP1 [4]
ABCB1 [3]
ARID2 [3]
GATA2 [3]
GNAS [3]
Complex karyotype [2]
EP300 [2]
* P < 0.05
· P < 0.1
-log10(P-value)
>3 (Co-occurence)
2
1
0
1
2
> 3 (Mutually exclusive)


A
CCyR
RUNX1wt (n = 73, 89%)
RUNX1mut (n = 9, 11%)
Fine-Gray p-value = 0.006
Cumulative incidence
Months
B
MMR
RUNX1wt (n = 73, 89%)
RUNX1mut (n = 9, 11%)
Fine-Gray p-value = 0.015
Cumulative incidence
Months
C
MR4.0
RUNX1wt (n = 73, 89%)
RUNX1mut (n = 9, 11%)
Fine-Gray p-value = 0.061
Cumulative incidence
Months
D
CCyR
KMT2Dwt (n = 78, 95%)
KMT2Dmut (n = 4, 5%)
Fine-Gray p-value = 0.096
Cumulative incidence
Months
E
MMR
KMT2Dwt (n = 78, 95%)
KMT2Dmut (n = 4, 5%)
Fine-Gray p-value = 0.102
Cumulative incidence
Months
F
MR4.0
KMT2Dwt (n = 78, 95%)
KMT2Dmut (n = 4, 5%)
Fine-Gray p-value = 0.185
Cumulative incidence
Months
G
TFS
Log-rank p-value < 0.001
RUNX1wt (n = 73, 89%)
RUNX1mut (n = 9, 11%)
Probability
Months
H
TFS
Log-rank p-value = 0.077
STAT5Awt (n = 77, 94%)
STAT5Amut (n = 5, 6%)
Probability
Months

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

Mengyao Yuan, Li Zhou, Weiming Li, Xin Du, Jianyu Weng, Linhua Yang, Yanping Ma, Bingcheng Liu, Zhenfang Liu, Qin Wen, Shasha Zhao, Yanli Zhang, Qingxian Bai, Xianqi Feng, Yanqiu Han, Chunshui Liu, Li Meng, Baohong Wang, Xuehong Ran, Xiaodong Wang, Haiguo Zhang, Yun Zeng, Qing Leng, Lu Yu, Zongru Li, Robert Peter Gale, Xiaojun Huang, and Qian Jiang

Mengyao Yuan, Li Zhou and Weiming Li contributed equally to this study.
Correspondence: Qian Jiang

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)	-	-	-	-	-	-	-	-	-	-	-	-

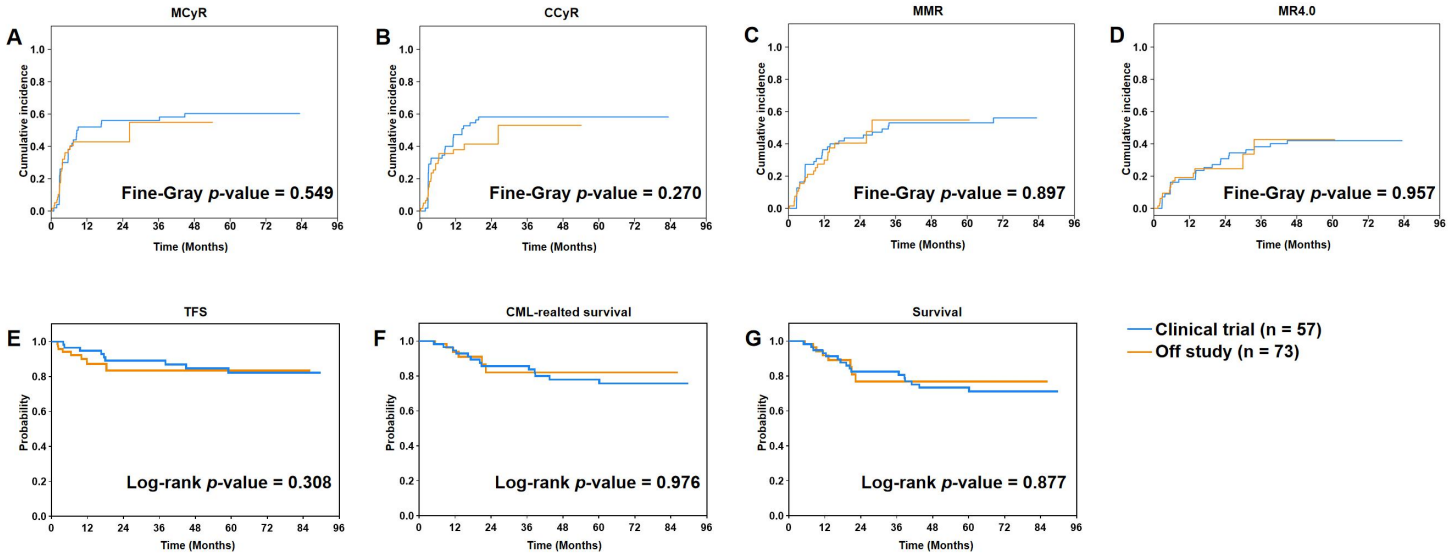
ACAs, additional cytogenetic abnormalities; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CI, confidence interval; HR, hazard ratio; MCyR, major cytogenetic response; mo, months; MMR, major molecular response; MR4.0, molecular response 4.0; QOD, 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.

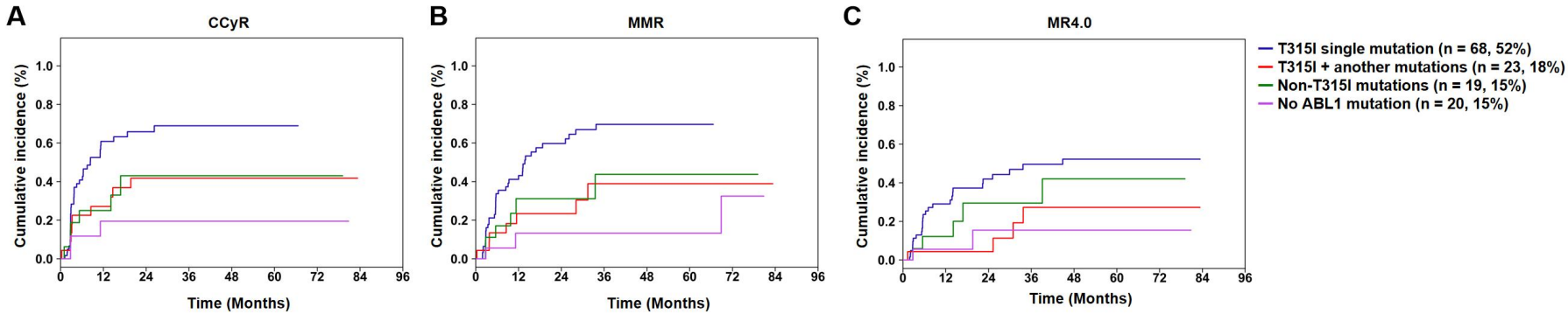
#All subjects harboring *RUNX1* or *KMT2D* variant did not achieve CCyR, MMR or MR4.0.

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

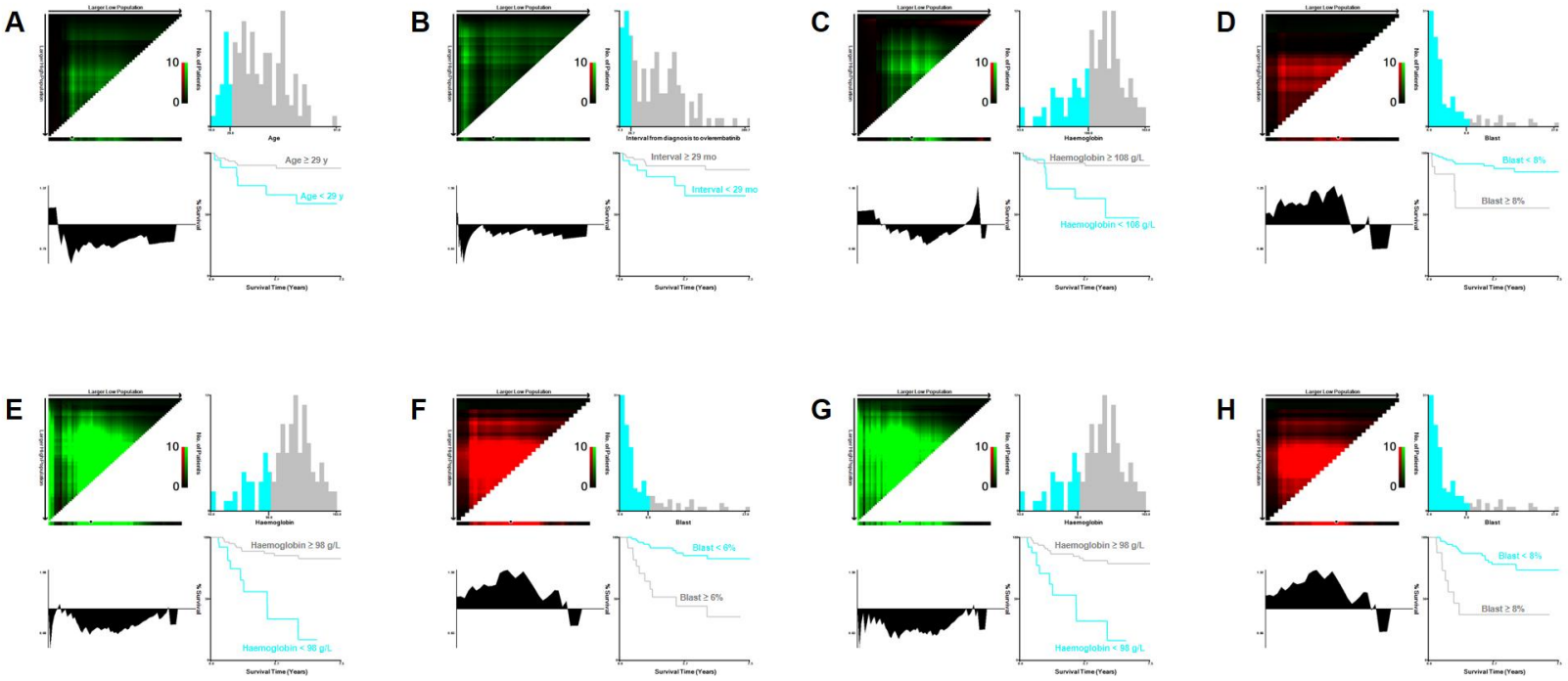
Co-variates listed without corresponding values were included in the initial multi-variable Cox model but excluded during the final stepwise selection; therefore, hazard ratios and *p*-values are not reported for them.



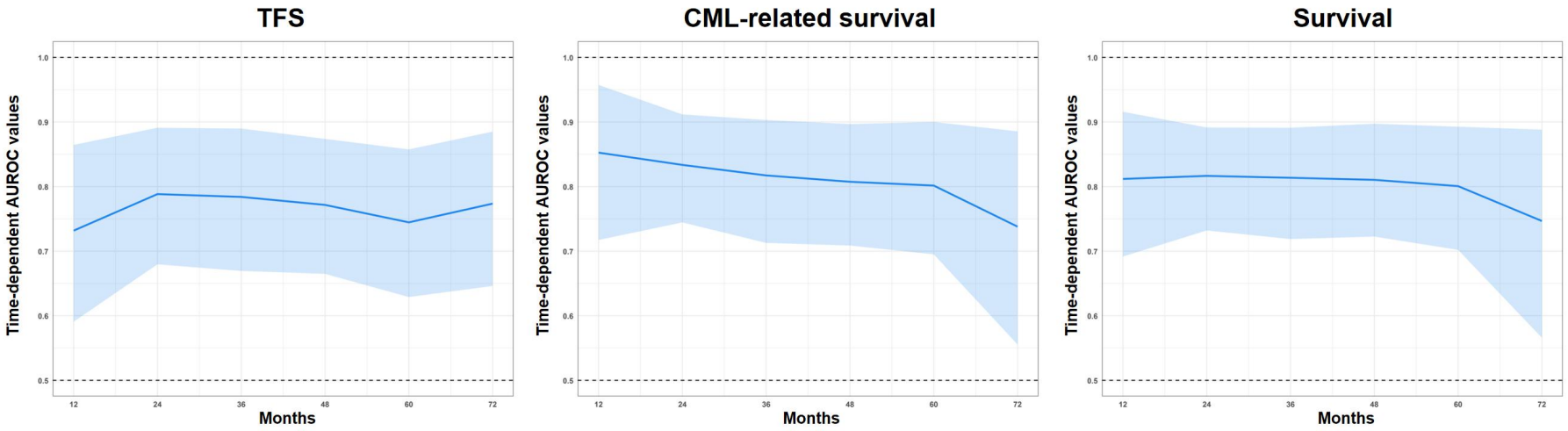
Supplement Figure 1. Comparison of therapy responses and outcomes between the clinical trial cohort and off-study cohort. (**A-D**) Therapy responses; (**E-G**) Outcomes. MCyR, major cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; MR4.0, molecular response 4.0;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



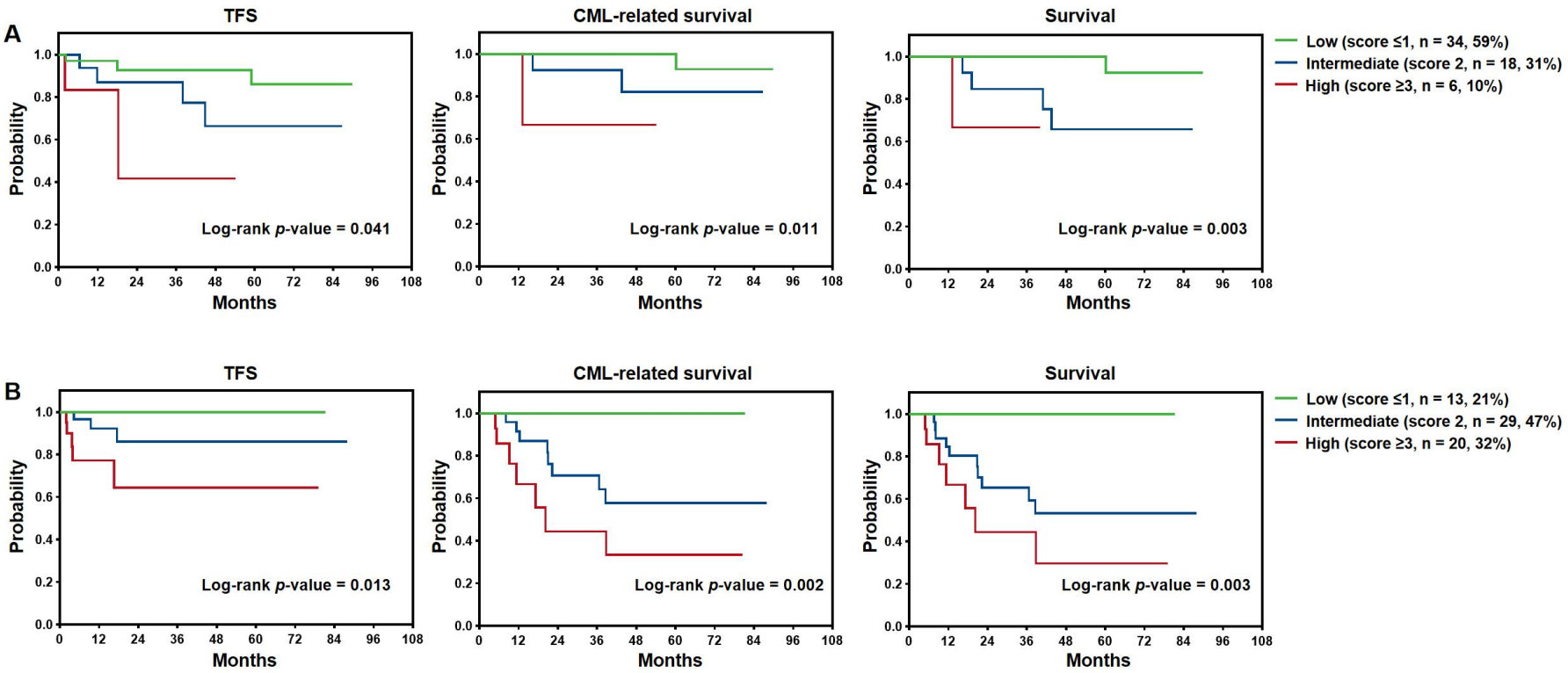
Supplement Figure 2. Responses of olverembatinib by baseline *BCR::ABL1* mutation status in subjects with accelerated phase CML failing prior TKI. (**A**) CCyR, complete cytogenetic response; (**B**) MMR, major molecular response; (**C**) MR4.0, molecular response 4.0.



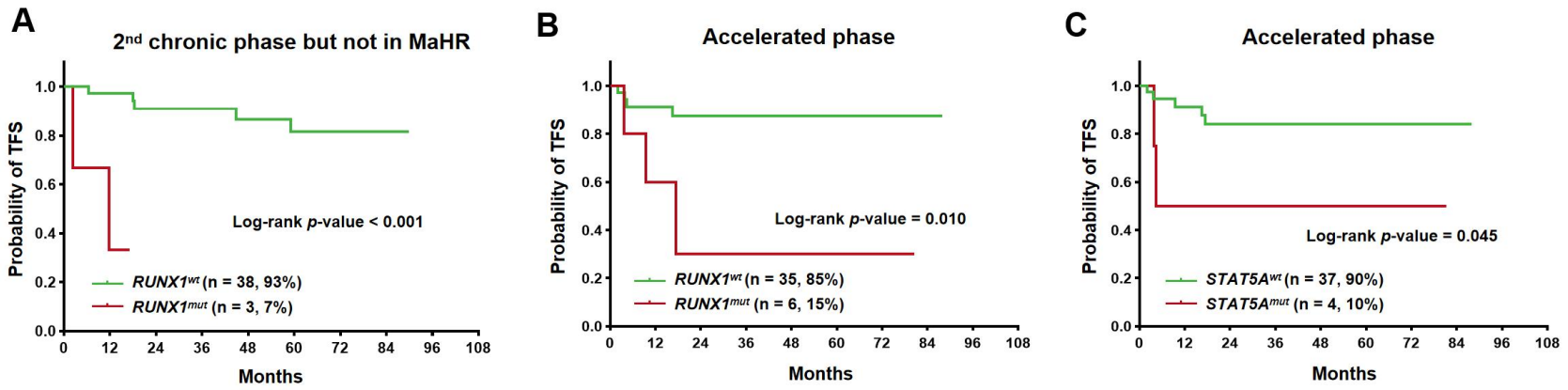
Supplement Figure 3. X-tile analyses to determine the optimal cut-off values of outcomes for continuous co-variates in survival analyses. **(A-D)** For transformation-free survival; **(E-F)** For CML-related survival; **(G-H)** For survival.



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.