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

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## 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. Sixty-two were in second chronic phase. All failed ≥1 tyrosine kinase inhibitor (TKI) 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, major molecular response and molecular response 4.0 were 59% (95% confidence interval [CI]: 49- 69), 53% (95% CI: 42-62), 52% (95% CI: 41-62) and 42% (95% CI: 31-53), respectively. The 6-year probabilities of transformation-free survival (TFS), CML-related survival and survival were 81% (95% CI: 72-90), 76% (95% CI: 67-87%) and 71% (95% CI: 61-82), respectively. In multi-variable analyses, an interval from diag-

nosis of CML to olverembatinib start <29 months, failure to achieve complete hematologic response 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.

# 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 second-or third-generation tyrosine kinase inhibitors (2G- or 3G-TKI).[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 covariates correlated with outcomes.

# Methods

We reviewed the medical records of 130 subjects receiving olverembatinib for accelerated-phase CML from June, 2017 to October, 2024 at 20 Chinese centers. The inclusion criteria were as follows: (i) CML subjects in accelerated-phase or second chronic-phase but not in major hematologic response (MaHR); (ii) failure of ≥1 prior TKI-therapies (including T315I mutation); (iii) no prior history of blast phase. Fifty-seven subjects were enrolled in phase-I/-II trial of olverembatinib.[12] Covariates including sex, age, co-morbidities, prior TKI 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 (TRAE) during olverembatinib therapy were collected. Comorbidity(ies) were classified using the Charlson Comorbidity Index.[14,15] Dose adjustments were based on responses and/or TRAE, guided by clinical protocols for clinical trial cohorts and European LeukemiaNet (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 made using ELN recommendations.[16,17] Criteria for accelerated phase include ≥1 of the following: (i) blood or bone marrow blasts ≥15% but <30%; (ii) blood or bone marrow blasts and promyelocytes ≥30% with blasts <30%; (iii) blood basophils ≥ 20%; (iv) platelet concentration <100×10$^9$/L unrelated to therapy; (v) additional chromosome abnormalities (ACA) in Philadephia-chromosome-positive (Ph$^+$) cells, major route on treatment.[16,17] MaHR was defined as complete hematologic response (CHR) or no evidence of leukemia.[12,18] High-risk ACA included +8, a second 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]

TRAE 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 TRAE.

### 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 (*Online Supplementary Methods*). Candidate genes in the targeted sequencing panels are displayed in *Online Supplementary Table S1*.

### Statistics

Pearson $\chi^2$ 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

One hundred and thirty subjects were studied. The last follow-up was March 2, 2025. The median follow-up was 28 months (interquartile range [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 (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 second 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). Sixty-one (47%) subjects received two prior TKI and 48 (37%), ≥3 prior TKI. One hundred and twenty-five subjects (96%) had e13a2 and/or e14a2 BCR::ABL1 transcripts and five (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%) at 30 mg; 84 (65%) at 40 mg and nine (7%) at 50 mg. One hundred and 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 me-

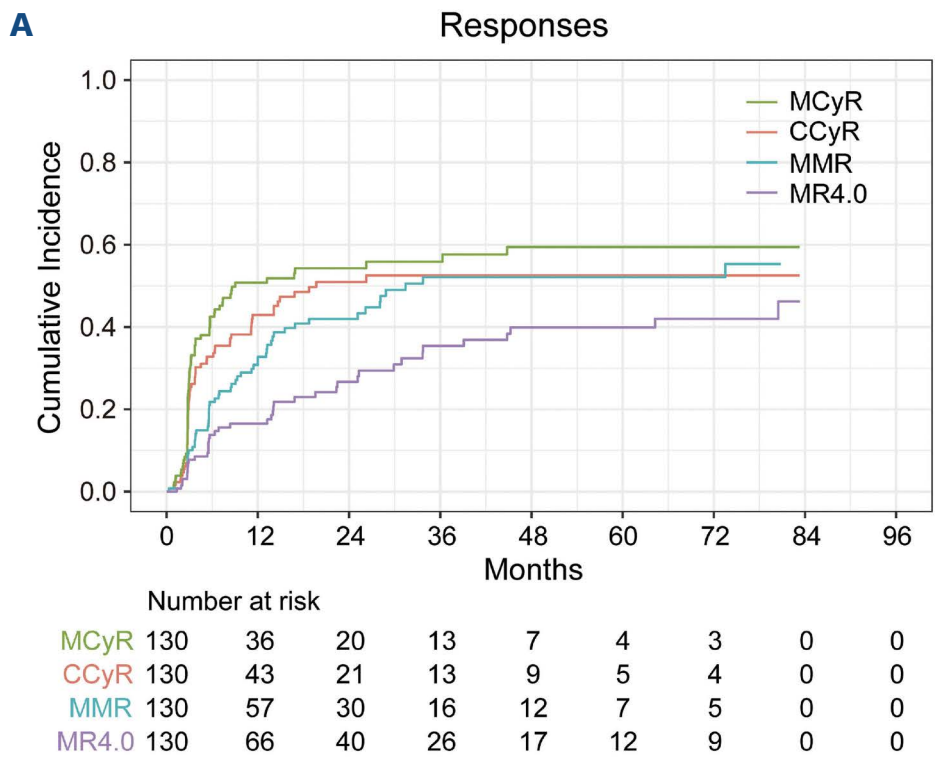
**Table 1.** Subject covariates.

| Covariates | Total, N=130 |
|---|---|
| Age at diagnosis of CML, years, median (IQR) | 37 (26-50) |
| Age at the start of olverembatinib therapy, years, median (IQR) | 43 (34-57) |
| Male, N (%) | 93 (72) |
| Phase at diagnosis, N (%)<br>Chronic phase<br>Accelerated phase | <br>101 (78)<br>29 (22) |
| BCR::ABL transcript, N (%)<br>*e13a2 and/or e14a2*<br>Uncommon transcripts | <br>125 (96)<br>5 (4) |
| Comorbidity, N (%) | 41 (32) |
| Interval from diagnosis of CML to olverembatinib therapy, month, median (IQR) | 72 (25-121) |
| N of lines of prior TKI-therapy, N (%)<br>1<br>2<br>≥3 | <br>21 (16)<br>61 (47)<br>48 (37) |
| Best therapy response on prior TKI therapy, N (%)<br>No CHR<br>CHR<br>CCyR<br>MMR<br>MR4.0<br>Unknown | <br>30 (23)<br>63 (48)<br>10 (8)<br>16 (12)<br>6 (5)<br>5 (4) |
| Phase at the start of olverembatinib therapy, N (%)<br>2nd chronic phase*<br>Accelerated phase<br>Blasts 15-29%<br>Basophils ≥20%<br>Major route ACA/Ph+<br>Platelet concentration <100x10$^9$/L unrelated to therapy<br>≥2 covariates | <br>62 (48)<br><br>5 (4)<br>23 (18)<br>25 (19)<br>2 (2)<br>13 (10) |
| WBC, ×10$^9$/L, median (range) | 7 (2-300) |
| Hemoglobin, g/L, median (range) | 118 (43-163) |
| Platelets, ×10$^9$/L, median (range) | 186 (12-2,999) |
| 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 (%)<br>No *ABL1* mutation<br>T315I single mutation<br>T315I + another mutations<br>Non-T315I mutations | <br>20 (15)<br>68 (52)<br>23 (18)<br>19 (15) |
| ACA Ph+, N (%)<br>High-risk, N (%)<br>Complex aberrant karyotype, N (%)<br>+8, N (%)<br>+Ph, N (%)<br>i(17q), N (%)<br>–7/del(7q), N (%) | 41 (33)<br>27 (21)<br>19 (15)<br>15 (12)<br>10 (8)<br>7 (6)<br>5 (4) |

*At olverembatinib initiation, 62 subjects (48%) were in the 2nd chronic phase but not in major hematologic response (MaHR). ACA: additional chromosome abnormalities; CHR: complete hematologic response; CML: chronic myeloid leukemia; CCyR: complete cytogenetic response; IQR: interquartile range; MMR: major molecular response; MR4.0: molecular response 4.0; Ph: Philadelphia chromosome; TKI: tyrosine kinase inhibitor; WBC: white blood cells.

dian 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% (95% CI: 42-62), 52% (95% CI: 41-62), and 42% (95% CI: 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 (CVE) (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% (95% CI: 72-90), 76% (95% CI: 67-87) and 71% (95% CI: 61-82; Figure 1B), respectively. Treatment responses and outcomes were similar between the clinical trial and the off-study cohorts (*Online Supplementary Figure S1*).

At the last follow-up, 79 (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), TRAE (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.



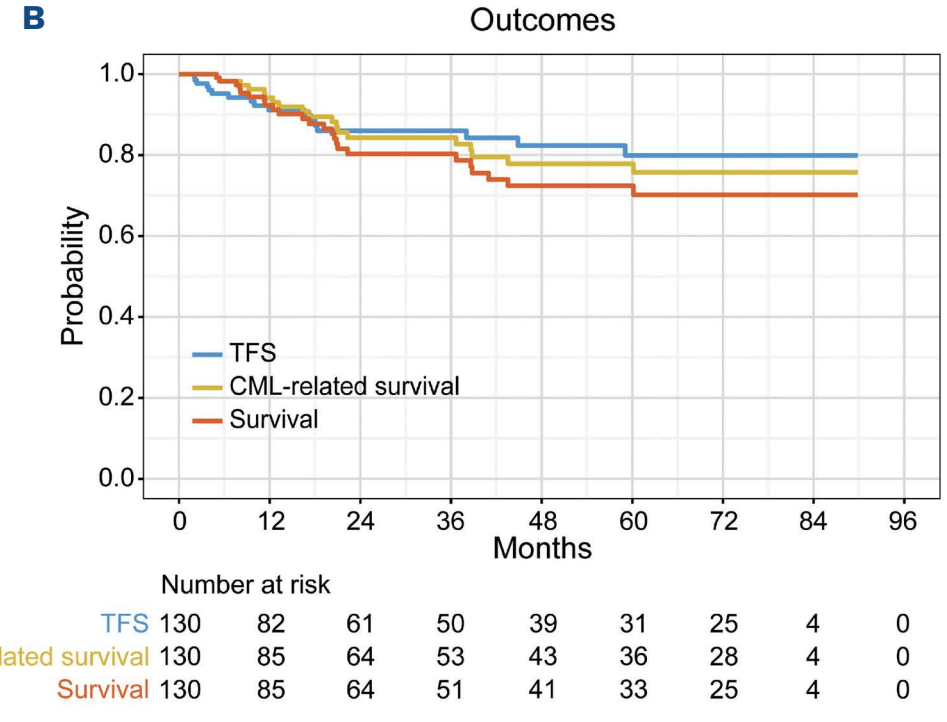




**Figure 1. Responses and outcomes.** (A) Responses. (B) Outcomes. MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; MR4.0: molecular response 4.0; TFS: transformation-free survival.

**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* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| 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, month (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 ACA (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 | - | - | - | - |

ACA: additional cytogenetic abnormalities; CCyR: complete cytogenetic response; CML: chronic myeloid leukemia; CI: confidence interval; HR: hazard ratio; MCyR: major cytogenetic response; MMR: major molecular response; MR4.0: molecular response 4.0; ref: reference; 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-related survival, or survival, best prior TKI-therapy responses ≥ CHR *versus* < CHR.

### Co-variates associated with responses and outcomes

Results of univariable analyses are displayed in *Online Supplementary Table S2*. 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 (Table 2; *Online Supplementary Figure S2*). 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 ACA ($P$=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 second 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 *Online Supplementary Figure S3*. 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 ACA ($P$=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 three risk prognostic cohorts: (i) low- (score ≤1; N=47, 39%); (ii) intermediate- (score 2; N=47, 39%) and high-risk (score ≥3; N=26, 22%). The corresponding 6-year probabilities of TFS were 89% (95% CI: 78-100), 77% (95% CI: 63-95) and 59% (95% CI: 36-80; $P$=0.004), respectively; CML-related survival, 94% (95% CI: 84-100), 67% (95% CI: 52-87) and 38% (95% CI: 18-72; $P$<0.001), respectively and survival, 94% (95% CI: 83-100), 58% (95% CI: 43-78) and 36% (95% CI: 16-69; $P$<0.001; Figure 2A-C), respectively. Time-dependent AUROC 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 AUROC of 0.73-0.85 (Figure 2D-F; *Online Supplementary Figure S4*).

We evaluated the outcomes by the risk prognostic group in the accelerated phase and second 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; *Online Supplementary Figure S5*).

### 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 3A). 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;

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

| Covariates using category variables | TFS | | CML-related survival | | Survival | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Interval from diagnosis to olverembatinib start <29 months (ref ≥29 months) | 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 ACA (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 | - | - | - | - |

ACA: additional cytogenetic abnormalities; CHR: complete hematologic response; CML: chronic myeloid leukemia; CI: confidence interval; HR: hazard ratio; MCyR: major cytogenetic response; ref: reference; TFS: transformation-free survival; TKI: tyrosine kinase inhibitor.

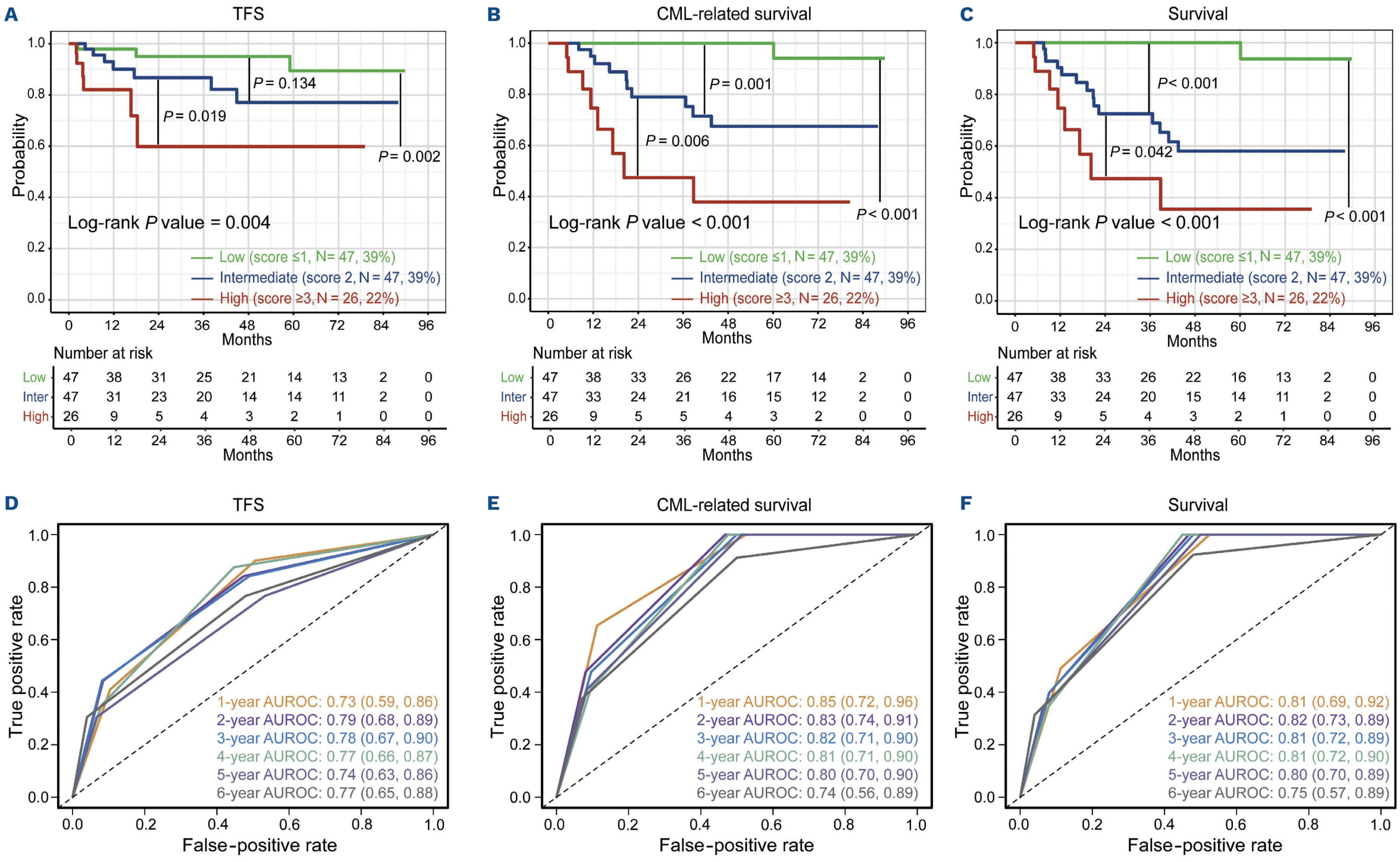



**Figure 2. Prognostic value of the risk group by the number of adverse prognostic covariates.** (A-C) Kaplan-Meier curves of transformation-free survival (TFS), chronic myeloid luekemia (CML)-related survival, and survival. (D-F) ROC curves of the risk group for 1-, 2-, 3-, 4-, 5- and 6-year probabilities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

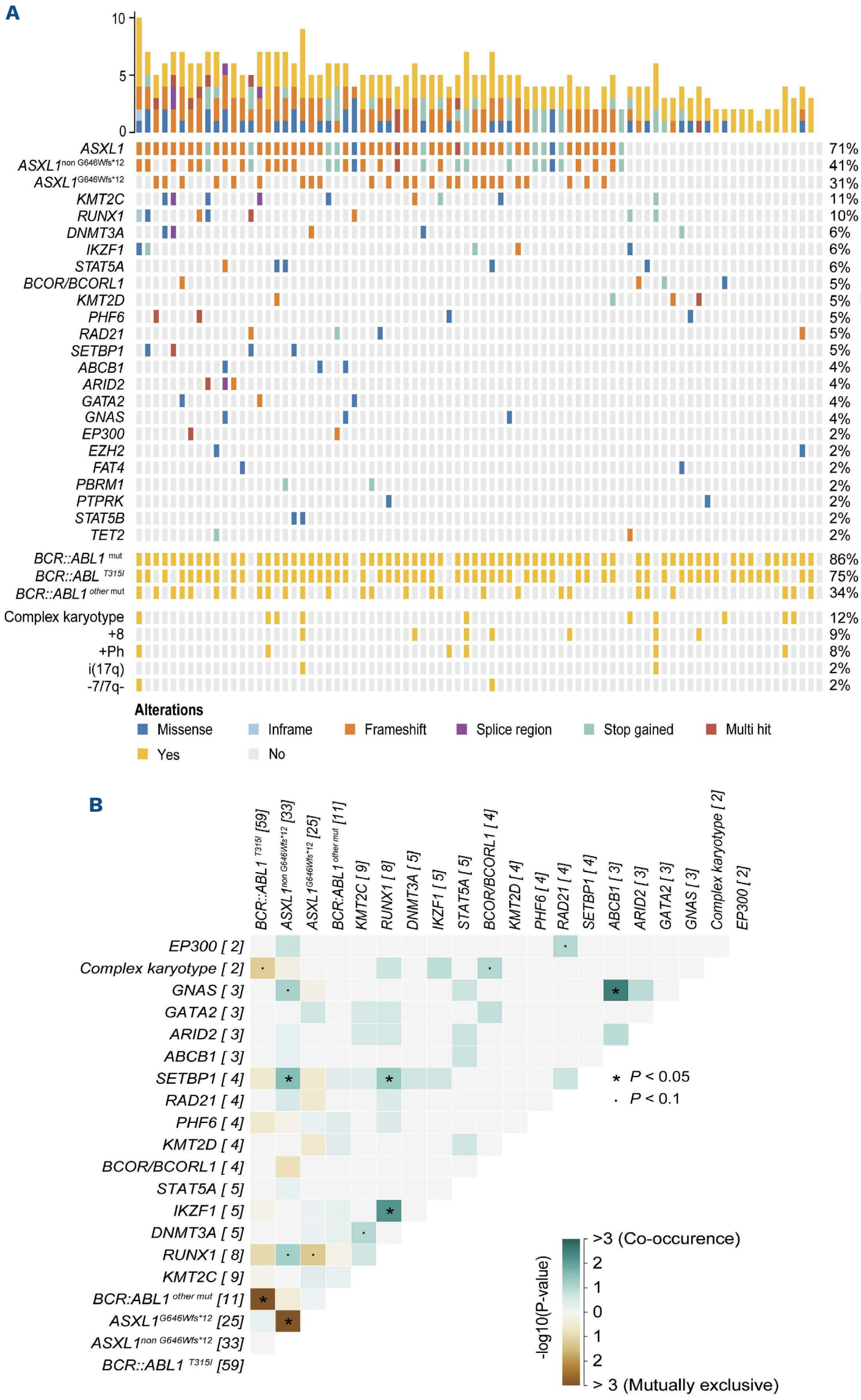



**Figure 3. Variant profiles.** (A) Variant distribution. (B) Pair-wise associations between cytogenetics and/or genomics.

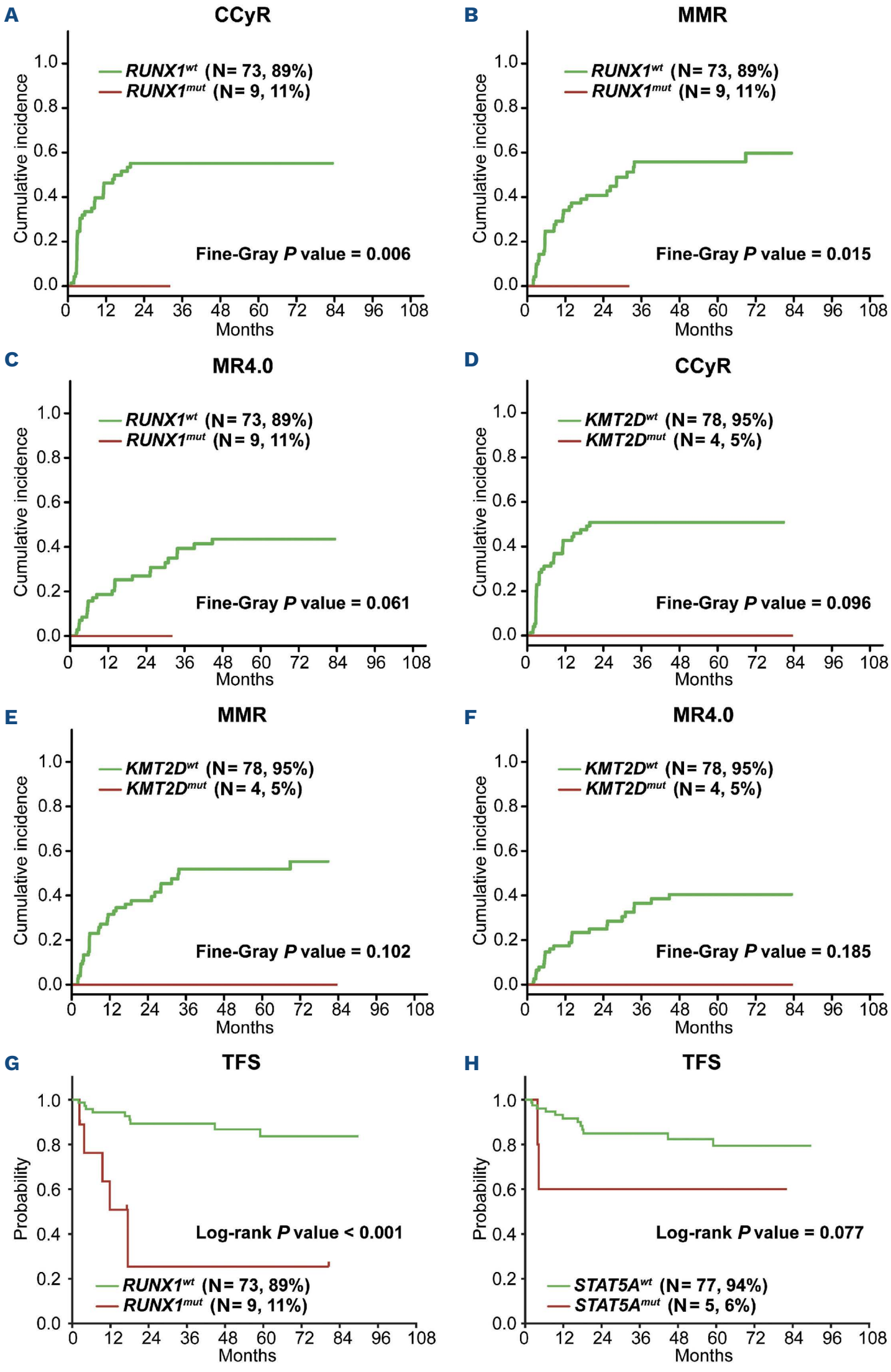



**Figure 4. Impact of variants on subsequent cytogenetic and molecular response, and transformation-free survival.** (A-C) *RUNX1* variant on cumulative incidence of complete cytogenetic response (CCyR), major molecular response (MMR) and molecular response 4.0 (MR4.0). (D-F) *KMT2D* variant on cumulative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

*P*=0.003; Figure 3B).

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 4A-F). In multivariable analyses *RUNX1* variants (hazard ratio [HR]=9.4; 95% CI: 2.7-33.2; *P*<0.001) and *STAT5A* variants (HR=6.3; 95% CI: 1.2-33.9; *P*=0.030) were significantly-associated with worse TFS but not CML-related survival or survival (Figure 4G, H; *Online Supplementary Table S3)*. 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 the second chronic phase but not in MaHR cohort (*Online Supplementary Figure S6*). The impact of the *STAT5A* variant on outcomes was not assessed in the second chronic phase

**Table 4.** Treatment-related adverse events: subjects with event/evaluable subjects.

| **Hematologic TRAE** | **Grade ≥3, N (%)** | **Grade ≥4, N (%)** |
|---|---|---|
| Thrombocytopenia | 50/124 (40) | 37/124 (30) |
| Leukopenia | 19/124 (15) | 6/124 (5) |
| Neutropenia | 15/124 (12) | 8/124 (6) |
| **Non-hematologic TRAE** | **Any grades, N (%)** | **Grade ≥2, N (%)** |
| 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. TRAE: treatment-related adverse events.

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 hyperpigmentation (N=65, 53%), followed by hypertriglyceridemia (N=46, 38%), proteinuria and hypocalcemia (N=39, 32% each; Table 4). CVE 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. TRAE 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-TKI 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 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 blast-phase CML, 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 CVE is a critical safety concern during 3G-TKI treatment. In this study, the incidence of CVE 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 *vs*. 60 years). Other potential reasons include the shorter median follow-up period in our study (28 *vs*. 32 months) and the smaller proportion of subjects with hypertension comorbidities before olverembatinib initiation (14% *vs*. 47%). It is imperative that future clinical practice will focus on the surveillance of CVE 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.

### Disclosures

*RPG is a consultant for Antengene Biotech LLC and Shenzen TargetRx; is a medical director at FFF Enterprises Inc.; discloses speaker's bureau for Janssen Pharma, BeiGene and Hengrui Pharma; is on the board of directors at Russian Foundation for Cancer Research Support and is on the scientific advisory board of StemRad Ltd. All other auhors have no conflicts of interest to disclose.*

### 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 version of the manuscript, take responsibility for the content and agreed to publication.*

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

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