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A lower-intensity, venetoclax-containing protocol is effective in adults with newly diagnosed mixed-phenotype acute leukemia

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Running heads: Venetoclax-containing protocol as induction therapy for mixed-phenotype acute leukemia

Author Contributions

Xiang Zhang, Depei Wu and Jia Chen were responsible for designing and writing the protocol. Ying Zhang and Yi Fan contributed to writing and editing the manuscript. Mimi Xu was responsible for collecting, analyzing and interpreting the data. Shengli Xue, Xiaowen Tang, Huiying Qiu, Miao Miao, Suning Chen, Haixia Zhou, Jian Zhang, Xiaofei Yang and Yang Xu were responsible for patient care and data assurance. All authors gave final approval of the manuscript and agreed to be accountable for all aspects of the work.

Data-sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest The authors declare that they have no competing interests.

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To the Editor:

Mixed-phenotype acute leukemia (MPAL) is a rare type of leukemia characterized by the expression of markers of more than one lineage, including B-lymphoid, T-lymphoid, and myeloid lineages[1]. Patients with MPAL have dismal outcomes, and no optimal treatment strategy has yet been established. Available study data indicate that allogeneic hematopoietic stem cell transplantation (allo-HSCT) may improve patient prognosis[2,3]. However, traditional intensive chemotherapy relies on nonspecific cytotoxic drugs, which may lead to multiorgan toxicity and treatment discontinuation, potentially rendering patients ineligible for transplantation. In recent years, lower-intensity regimens of venetoclax and azacitidine (ven-aza) have been widely adopted for treating acute myeloid leukemia (AML) across diverse patient populations, including elderly patients, those who are unfit for intensive chemotherapy, and some younger patients. These regimens are well tolerated and effective, with reported response rates of 60%–80%[4,5]. Emerging evidence also supports the therapeutic potential of ven-aza for patients with acute lymphoblastic leukemia (ALL)[6]. Furthermore, blinatumomab has emerged as a promising treatment for B-cell ALL and has demonstrated favorable efficacy and safety[7]. Currently, the toxicity profiles and efficacy of these lower-intensity regimens in MPAL remain unclear. A limited number of case reports suggest potential efficacy[8-10], and more evidence is needed. Here, we report the efficacy and toxicity of a lower-intensity, venetoclax-containing protocol as induction therapy for patients with newly diagnosed MPAL.

This study included a total of 16 patients with newly diagnosed MPAL who were treated

at the First Affiliated Hospital of Soochow University between July 2021 and October 2023. The patients were retrospectively recruited following approval from the institutional ethics committee (approval number: 2024749). All enrolled patients received a lower-intensity, venetoclax-containing induction regimen, with 100 mg venetoclax (orally) on day 1, 200 mg on day 2, and 400 mg on days 3 to 28, and azacitidine (75 mg/m^2 subcutaneously) on days 1 to 7. The dosage of venetoclax was modified according to the prescribing information when it was coadministered with strong or moderate CYP3A inhibitors. Tyrosine kinase inhibitors (TKIs) were administered orally to patients with *BCR-ABL1* fusion. Blinatumomab was recommended for patients with B-lineage MPAL. For patients at a high risk of febrile neutropenia or severe, persistent neutropenia, antimicrobial prophylaxis comprising oral fluoroquinolones and posaconazole was administered. Central nervous system (CNS) prophylaxis was performed via lumbar puncture with the intrathecal administration of methotrexate, cytarabine, and dexamethasone. Treatment efficacy was evaluated after the first induction cycle, per the European Leukemia Network (ELN) guidelines[11]. Measurable residual disease (MRD) was assessed through multiparameter flow cytometry, with MRD negativity defined as a level less than 1×10^{-4}. For patients who were *BCR-ABL1* fusion-positive (*BCR-ABL1*$^+$), *BCR-ABL1* transcripts were monitored through qPCR.

The median age of the 16 patients was 45 years (range 18–60 years). Six patients had MPAL *BCR-ABL1* fusion, 5 patients had MPAL B/myeloid, 4 patients had MPAL T/myeloid, and 1 patient had MPAL B/T. Eight patients presented with significantly

elevated white blood cell (WBC) counts (>30×10^9/L) at diagnosis, 5 of whom had WBC counts greater than 100×10^9/L. These patients received cytoreduction with leukapheresis, hydroxyurea, steroids or low-dose cytarabine until the WBC counts decreased to less than 25×10^9/L before induction. Molecular data were available for 15 patients, with gene mutations detected in 12 (80%) patients. No patients had extramedullary involvement at diagnosis. The detailed baseline characteristics are presented in **Table 1**.

As shown in **Figure 1,** all enrolled patients achieved remission after induction therapy, including 9 (56.3%) patients who achieved complete remission (CR) and 7 (43.7%) patients who achieved complete remission with incomplete blood count recovery (CRi). Eight (50%) patients achieved MRD negativity.

Adverse events were assessed in 16 patients during the induction period (**Supplementary Table S1**). The most common grade ≥3 treatment-related adverse events were hematological toxicities, including neutropenia (100%; 16/16), thrombocytopenia (87.5%; 14/16), and anemia (81.3%; 13/16). The median duration for neutrophil (>0.5×10^9/L) and platelet (>30×10^9/L) recovery were 21.5 and 19 days, respectively. The most common nonhematological toxicities were fatigue (62.5%), fever (31.3%), and nausea (18.8%). No incidence of tumor lysis syndrome was reported among the patients. The most common grade ≥3 nonhematological toxicity was infection (12.5%). No patients died during induction therapy.

Following one cycle of induction therapy, 3 patients received ven-aza-based

consolidation, 11 patients received standard-dose chemotherapy consolidation, and 2 patients received high-dose cytarabine-based consolidation. Ten patients underwent allo-HSCT during the first CR, all of whom maintained continuous CR by the end of follow-up. Only 1 recipient of allo-HSCT died due to pulmonary infection. Four patients experienced relapse, but all achieved second CR, and the median time to relapse after remission was 3.7 months (range 0.9–5.1 months). Patient 2 received ven-aza plus flumatinib followed by allo-HSCT. Patient 6 with CNS relapse received ven-aza plus ponatinib followed by allo-HSCT. Patient 11 received autologous HSCT bridging to CD19 CAR-T. Patient 12 had a FLT3 mutation and received ven plus gilteritinib.

The median follow-up period was 36.8 months (range 18.3–49.7 months), the median event-free survival (EFS) and overall survival (OS) were not reached, and the estimated 3.5-year EFS and OS were 68.8% and 87.5%, respectively (**Figure 2A and B**). At the last follow-up, two mortality events were recorded: one attributed to disease relapse and one to pulmonary infection.

Among the six patients with *BCR-ABL1*$^{+}$ MPAL, 83.3% presented with a WBC counts of >30×10^9/L and 66.7% had a WBC counts of >100×10^9/L. The expression of P190$^{bcr-abl}$ was more common than that of P210 $^{bcr-abl}$. Four patients were treated with flumatinib, one with dasatinib and one with imatinib. All six patients achieved a major molecular response (MMR), with a median time to MMR of 1.5 months (range: 0.4–5.9 months). The 3.5-year OS and EFS rates were 100% and 66.7%, respectively. Furthermore, no significant difference in 3.5-year EFS was observed between patients with *BCR-ABL1*$^{+}$

MPAL and those with *BCR-ABL1* fusion-negative MPAL (*BCR-ABL1*$^{-}$ MPAL) (p=0.78) (**Supplementary Figure S1**).

Our data revealed that the lower-intensity, venetoclax-containing protocol yields promising outcomes in MPAL, with a notably higher CR rate than that reported in adult patients in previous studies (less than 80%)[2,12,13]. Moreover, a promising long-term prognosis was observed in our study, especially in those who underwent allo-HSCT during remission, with a significantly improved EFS (p=0.033). These results further underscore the importance of allo-HSCT as a post-remission therapy in patients with MPAL[2].

Recently, AML with mixed phenotype (AML-MP) has been highlighted by the Memorial Sloan Kettering Cancer Center (MSKCC), which is defined as therapy-related AML or AML with myelodysplasia-related changes that exhibit a mixed phenotype[14]. AML-MP is immunophenotypically indistinguishable from MPAL but has a worse prognosis. Among their cohort of 55 patients with AML-MP, 20 patients were treated with hypomethylating agents alone or in combination with venetoclax, but none of them achieved CR or CRi. In our cohort, two patients with the B/myeloid phenotype met the criteria for AML-MP (Patients 7 and 8), and both of them achieved CR after induction of venetoclax-containing treatment. However, neither of the patients had adverse cytogenetic abnormalities nor TP53 mutations, which were frequently presented in the MSKCC report. Notably, one patient received blinatumomab due to high CD19 expression on leukemic cells, which may improve the treatment efficacy and suggests the potential of targeted therapies in patients with AML-MP.

Importantly, no patients developed severe complications that delayed subsequent treatment, and no treatment-related death was observed. We hypothesized that lower-intensity induction may alleviate myelosuppression and, therefore, decrease the risk of related adverse events including severe infection or bleeding. By contrast, intensive chemotherapy is associated with more severe toxicity profiles, which may lead to treatment interruption or even early death. For example, a study of 3728 patients with newly diagnosed AML who received intensive chemotherapy revealed 4-week mortality rates of 2%, 14%, and 50% in the low-, high-, and very high-risk groups, respectively[15]. The favorable safety and efficacy profile of the lower-intensity, venetoclax-containing protocol in our study supports a shift to lower-intensity, more targeted treatments for patients with MPAL. However, our study is limited by its retrospective nature, inconsistent regimens and small sample size.

In summary, our data demonstrate that the lower-intensity, venetoclax-containing induction regimen seems to be an effective and well-tolerated treatment for patients with MPAL. This regimen enables most patients to become eligible for individualized postinduction treatment and improves long-term prognosis. Given the limitations of our study, these findings need to be validated through well-designed randomized trials and real-world data.

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Table 1 Characteristics of patients with MPAL

Case	Age/ Gender	ECOG ps	WBC ($\times 10^9$/L)	MPAL type	Cytogenetics	Somatic mutations	Induction treatment
1	45/F	2	115.5	*BCR-ABL1* fusion	46,XX,der(9)?inv(9)(p11;q13) t(9;22)(q34;q11)der(22) t(9;22)(q34;q11)[10]	CEBPA	VA+TKIs
2	29/F	1	267.3	*BCR-ABL1* fusion	46,XX,der(5)ins(5;?), t(9;22)(q34;q11)[8] /46,XX,t(9;22)(q34,q11), 19p+[2]	RUNX1	VA+TKIs
3	25/F	1	313.8	*BCR-ABL1* fusion	46,XX,t(9;22)(q34;q11)[1] /46,XX[8]	(-)	VA+TKIs
4	50/M	1	35.8	B/myeloid	46,XY,add(2)(p25)[12] /46,XY[2]	BRAF, ARID2, IL-17R	V+BiTE
5	48/M	1	4.8	B/T	46,XY[20]	ASXL1, RNUX1, EZH2, NOTCH1, JAK1, JAK3, NRAS	VA+BiTE
6	51/F	1	344.0	*BCR-ABL1* fusion	Low mitotic activity	(-)	VA+TKIs
7	43/M	1	2.1	B/myeloid	46,XY,del(20)(q12;q13)[7] /46,XY[3]	FLT3, U2AF1, WT1, TYK2,	V+BiTE
8	45/F	2	48.8	B/myeloid	Low mitotic activity	STAG2	VA
9	35/M	1	2.7	T/myeloid	46,XY[20]	CXCR4, WT1, GATA2, KMT2D	VA
10	59/M	1	3.3	T/myeloid	45,XY,dic(21;22)(p11;p11)[10]	CEBPA, BCORL1, BRCA2, STAT3, ERBB3, KMT2A, SETD2	VA
11	18/F	2	25.8	B/myeloid	46,XX[20]	Missing	VA
12	60/F	2	140.3	B/myeloid	46,XX,t(10;11)(q12;q23)[9] /46,XX[1]	FLT3, IDH1,RUNX1	VA+BiTE

13	26/M	1	1.3	T/myeloid	46,XY[20]	NRAS, WT1, BRAF, IDH1, ASXL2 EP300, KDM6A, SETD2, ZBTB7A	VA
14	58/M	1	1.0	T/myeloid	46,XY,inv(16)(p13;q22)[2] /46,XY[2]	KRAS, ATM, ARC, FAT1	VA
15	52/F	2	13.6	*BCR-ABL1* fusion	46,XX,t(9;22)(q34;q11)[10]	(-)	VA+TKIs
16	35/M	2	36.8	*BCR-ABL1* fusion	46,XY,t(9;22)(q34;q11)[8] /45,idem,-7[2]	RUNX1	VA+TKIs

MPAL: mixed-phenotype acute leukemia, F: female, M: male, ECOG PS: Eastern Cooperative Oncology Group Performance Status, WBC: white blood cells, V: venetoclax, A: azacitidine, TKIs: tyrosine kinase inhibitors, BiTE: blinatumomab.

Figure legends

Figure 1. Swimmer plot of the dynamic response assessment. Sixteen patients achieved remission after induction therapy, including 9 (56.3%) patients who achieved CR and 7 (43.7%) patients who achieved CRi. Four patients experienced relapse, but all achieved a second CR. Two mortality events were recorded: one attributed to disease relapse and one attributed to pulmonary infection. CR: complete remission; CRi: complete remission with incomplete blood count recovery.

Figure 2. Survival of patients with MPAL. (A). Kaplan-Meier estimates of event-free survival. (B). Kaplan–Meier estimates of overall survival.

Figure 1

Click here to access/download;Figure;Figure 1.jpg

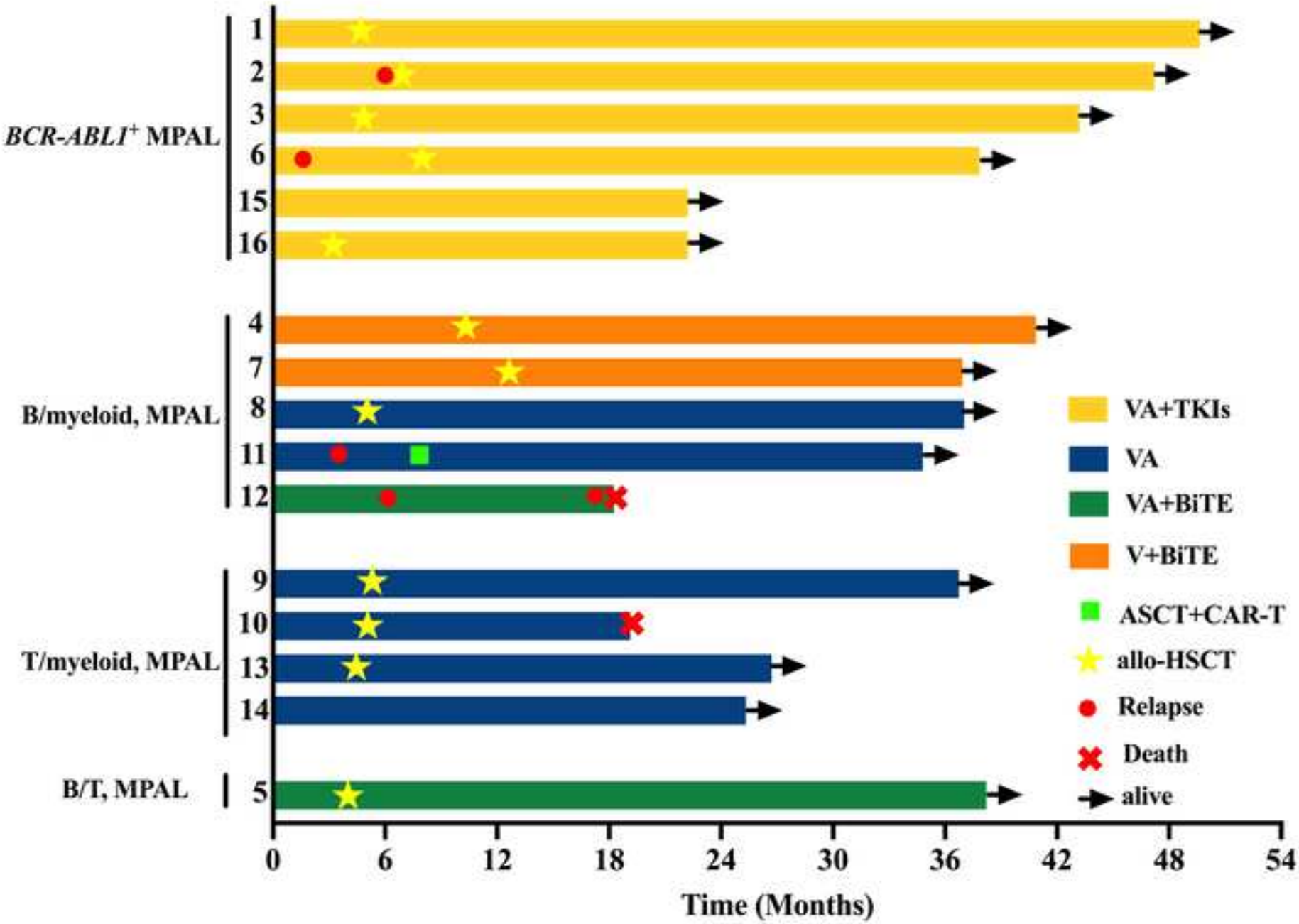
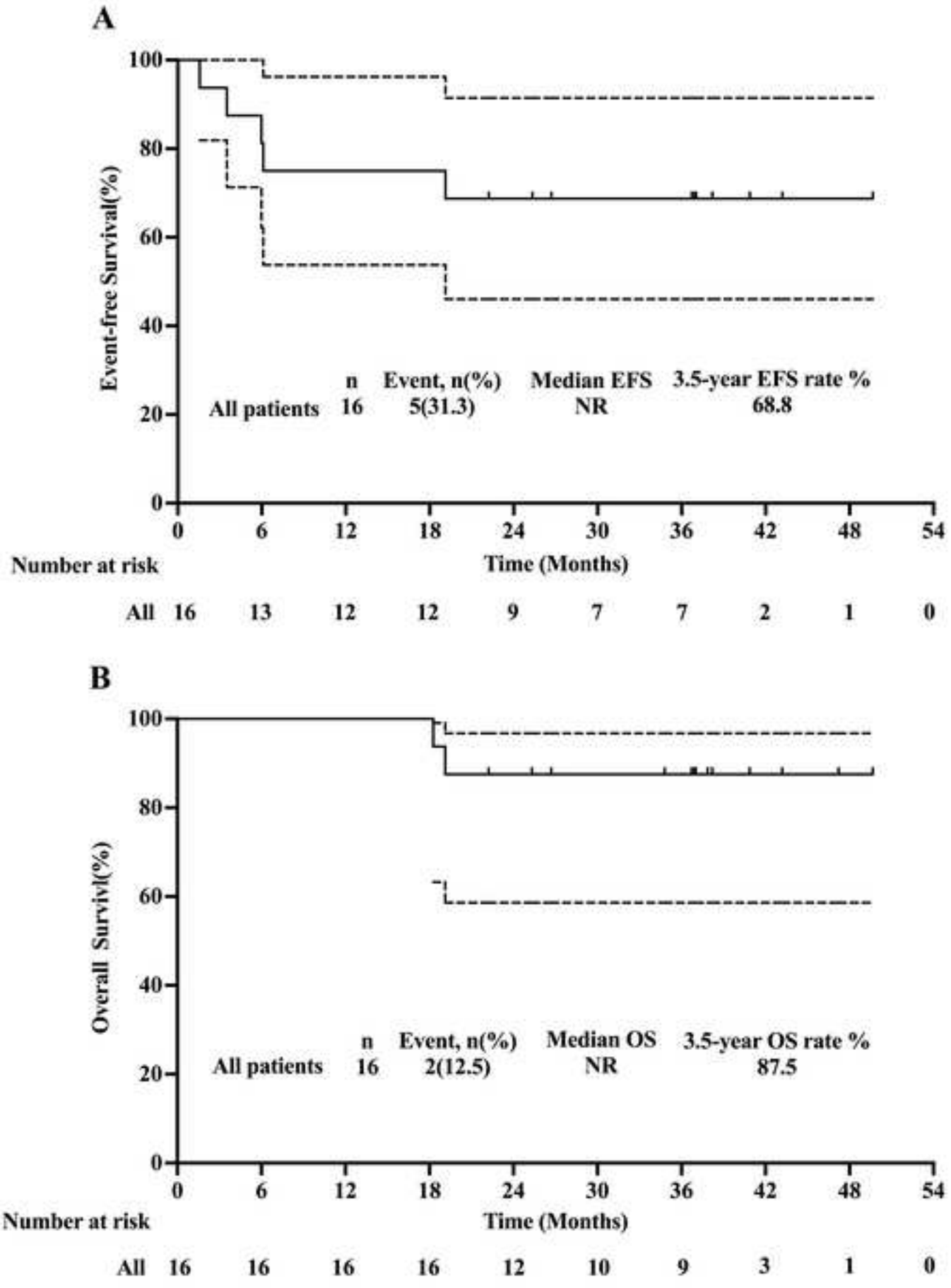
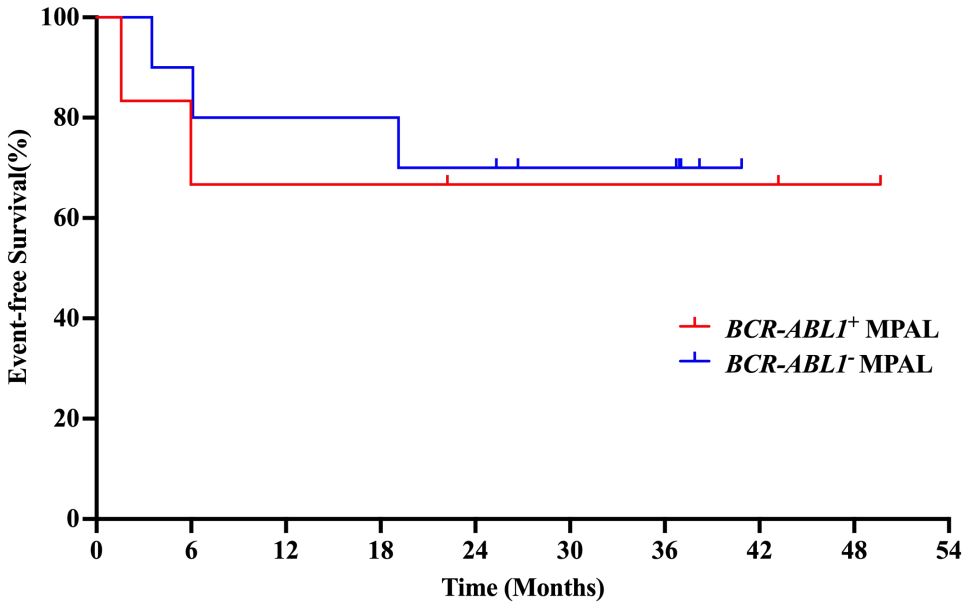


Figure 2



Supplementary Table S1 Adverse events

Adverse event	Any grade(n=16)	Grade≧3
Non-Hematological toxicity		
Pyrexia	5(31.3%)	0
Fatigue	10(62.5%)	0
Nausea	3(18.8%)	0
Vomiting	1(6.3%)	0
Diarrhea	1(6.3%)	0
Edema	1(6.3%)	0
Lung infection	1(6.3%)	1(6.3%)
Sepsis	1(6.3%)	1(6.3%)
Alanine aminotransferase increased	2(12.5%)	0
Glutamyl transpeptidase increased	2(12.5%)	0
Blood bilirubin increased	1(6.3%)	0
Creatinine increased	2(12.5%)	0
Hypokalemia	1(6.3%)	0
Hematological toxicity		
Anemia	16(100%)	13(81.3%)
Neutropenia	16(100%)	16(100%)
Thrombocytopenia	15(93.8%)	14(87.5%)



Supplementary Figure S1. **Kaplan–Meier estimates of the event-free survival.** There was no difference in 3.5-year EFS between *BCR-ABL1*$^{+}$ MPAL and *BCR-ABL1*$^{-}$ MPAL patients (P=0.78).