In patients with t(8;21) acute myeloid leukemia (AML), recurrent minimal residual disease (MRD) measured by RUNX1-RUNX1T1 transcript levels can predict relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT). This study aimed to compare the efficacy of preemptive interferon (IFN)-α therapy and donor lymphocyte infusion (DLI) in patients with t(8;21) AML following allo-HSCT. We also evaluated the appropriate method for patients with different levels of RUNX1-RUNX1T1 transcripts. In this retrospective study, consecutive patients who had high-risk t(8;21) AML and received allo-HSCT were enrolled. The inclusion criteria were as follows: (1) age ≤65 years; (2) regained MRD positive following allo-HSCT. MRD positive was defined as the loss of a ≥4.5-log reduction and/or <4.5-log reduction in the RUNX1-RUNX1T1 transcripts, and high-level, intermediate-level, and low-level MRDs were, respectively, defined as <2.5-log, 2.5−3.5-log, and 3.5−4.5-log reductions in the transcripts compared with the pretreatment baseline level. Patients with positive RUNX1-RUNX1T1 could receive preemptive IFN-α therapy or DLI, which was primarily based on donor availability and the intentions of physicians and patients. The patients received recombinant human IFN-α-2b therapy by subcutaneous injection twice a week every 4 weeks. IFN-α therapy was scheduled for six cycles or until the RUNX1-RUNX1T1 transcripts were negative for at least two consecutive tests. The rates of MRD turning negative for patients with low-level, intermediate-level, and high-level RUNX1-RUNX1T1 receiving IFN-α were 87.5%, 58.1%, and 22.2%, respectively; meanwhile, for patients with intermediate-level and high-level RUNX1-RUNX1T1 receiving DLI, the rates were 50.0% and 14.3%, respectively. For patients with low-level and intermediate-level RUNX1-RUNX1T1, the probability of overall survival at 2 years was higher in the IFN-α group than in the DLI group (87.6% vs. 55.6%;
Patients with a higher risk of relapse (11, 12). The MRD different levels of ef could benefit more from preemptive IFN-α therapy compared with DLI. Clinical outcomes were comparable between preemptive IFN-α therapy and DLI in patients with high-level RUNX1-RUNX1T1; however, they should be further improved.

**1 INTRODUCTION**

Acute myeloid leukemia (AML) with t(8;21) is a heterogeneous disease, and relapse can occur in 40–50% of patients treated with chemotherapy alone, even if it is considered to have a good prognosis (1, 2). Minimal residual disease (MRD) after chemotherapy can predict the relapse of t(8;21) AML (3–6), and allogeneic hematopoietic stem cell transplantation (allo-HSCT) can further decrease relapse and improve survival in patients with persistent RUNX1-RUNX1T1 after chemotherapy (5, 7–9). However, relapse remains experienced by nearly 20% of patients following allo-HSCT (10).

Regular monitoring of MRD after allo-HSCT can identify patients with a higher risk of relapse (11, 12). The MRD measured by the level of RUNX1-RUNX1T1 transcript has been identified as an effective predictor of relapse in patients with t(8;21) AML after allo-HSCT (13, 14). Therefore, intervention directed by MRD (i.e., preemptive intervention) is a rational option for relapse prophylaxis. One of the most critical immunotherapies after allo-HSCT is donor lymphocyte infusion (DLI) (15–17). Wang et al. (14) reported that preemptive DLI could prevent relapse and improve survival in patients with t(8;21) AML. Interferon-α (IFN-α) is another important immunotherapy after allo-HSCT (18–22); Mo et al. (20) reported that the survival of patients with MRD positive without any intervention was significantly lower than those receiving preemptive IFN-α therapy (20). Therefore, IFN-α therapy and DLI could improve the prognosis of patients with MRD following allo-HSCT. However, which preemptive intervention is more superior for t(8;21) AML patients receiving allo-HSCT is still unclear. Mo et al. (21) reported that the prognosis of preemptive DLI and IFN-α therapy was comparable, but their study included a small sample size of patients with t(8;21) AML. To date, no studies have compared the efficacy of preemptive DLI and IFN-α therapy in patients with t(8;21) AML.

Furthermore, we observed that RUNX1-RUNX1T1 transcript levels influenced the efficacy of preemptive IFN-α therapy; however, the influence of MRD levels on IFN-α therapy could not be further evaluated due to a small sample size of patients with higher levels of RUNX1-RUNX1T1 transcripts (20). In contrast, Wang et al. (14) reported that patients with a higher level of RUNX1-RUNX1T1 transcript could still benefit from DLI. Therefore, patients with different levels of RUNX1-RUNX1T1 transcript may benefit from different interventions. However, no studies have compared the efficacy of preemptive DLI and IFN-α therapy at different levels of RUNX1-RUNX1T1 transcript and the selection of appropriate preemptive interventions according to RUNX1-RUNX1T1 transcript levels remains unknown.

Therefore, this retrospective study aimed to compare the efficacy of preemptive DLI and IFN-α therapy in patients with t(8;21) AML following allo-HSCT. Furthermore, we also evaluated the appropriate intervention methods for patients with different levels of RUNX1-RUNX1T1 transcripts.

**2 METHODS**

**2.1 Patients**

Consecutive patients who had high-risk t(8;21) AML and received allo-HSCT at the Peking University Institute of Hematology (PUIH) were enrolled. The inclusion criteria were as follows: (1) were ≤65 years old (2) and regained MRD positive following allo-HSCT (5).

The exclusion criteria for IFN-α therapy were as follows: (1) active graft-versus-host disease (GVHD); (2) active and uncontrolled infections; (3) severe myelosuppression; (4) organ failure; and (5) hematologic relapse.

The exclusion criteria for DLI were as follows: (1) active GVHD; (2) active and uncontrolled infections; (3) organ failure; and (4) hematologic relapse (20).

One hundred and four patients were enrolled between October 1, 2013 and February 28, 2021 (Table 1). Forty-two patients were previously reported by Mo et al. (23), and in this study, they were followed up further. The endpoint analysis of the last follow-up was on September 1, 2021.

**2.2 Transplant Regimens**

Cytosine arabinoside, busulfan, cyclophosphamide (CY), and simustine were included in the preconditioning. The human leukocyte antigen (HLA)-unrelated donor (URD) and HLA-haploidentical donor (HID) groups received rabbit antithymocyte globulin (ATG, Supplementary Methods) (24–26). HID HSCT recipients received ATG and low-dose posttransplant CY (PTCY) for GVHD prophylaxis according to the protocol registered at http://clinicaltrials.gov/NCT02412423 (Supplementary Methods and Supplementary Figure S1) (24–28). Protocols for stem cell harvesting, donor selection, and HLA typing have been previously described in detail (29–32).
2.3 MRD Monitoring and Definition
The protocol for RUNX1-RUNX1T1 monitoring after allo-HSCT was performed according to the protocol of PUIH (5, 13). The definition of MRD positive was a loss of RUNX1-RUNX1T1 transcripts ≥4.5-log reduction and/or the <4.5-log reduction (20). Low-level, intermediate-level, and high-level MRD was defined as a reduction in transcripts of 3.5−4.5-log, 2.5−3.5-log, and <2.5-log, respectively, compared with the baseline level before treatment.

2.4 Protocol for Preemptive DLI and IFN-α Therapy
In this retrospective study, patients with positive RUNX1-RUNX1T1 received preemptive IFN-α therapy or DLI before hematologic relapse after allo-HSCT (12). The therapeutic option was primarily based on donor availability and the intentions of physicians and patients.

The patients received recombinant human IFN-α-2b therapy by subcutaneous injection twice a week every 4 weeks. IFN-α therapy was scheduled for six cycles or until the RUNX1-RUNX1T1 transcripts were negative for at least two consecutive tests (Supplementary Methods). IFN-α therapy could be prolonged upon the request of patients. IFN-α therapy was discontinued in patients with grade ≥3 toxicity, severe infection, severe GVHD, nonrelapse mortality (NRM), or relapse.

Granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells were administered instead of...
unstimulated donor blood lymphocytes. All patients received short-term immunosuppressive drugs after DLI. Patients could receive chemotherapy 48–72 h before DLI (i.e., chemo-DLI) (Supplementary Methods) (16, 17).

MRD status was regularly monitored at 1, 2, 3, 4.5, 6, 9, and 12 months after preemptive intervention and at 6-month intervals thereafter.

For patients with persistent and increasing levels of MRD (e.g., levels of RUNX1-RUNX1T1 transcripts increased by 1-log) or those who regained MRD positive after receiving MRD-negative status, if they were in the IFN-α group, they could be switched to the DLI group and vice versa (Figure 1).

2.5 Diagnosis and Therapy of GVHD After Preemptive Immunotherapy

GVHD diagnosis and therapy were based on common international criteria (33–38).

2.6 Definition and Assessment

Relapse was defined according to common international criteria (39). Patients who showed relapse were not considered to have MRD. NRM was defined as death without relapse or disease progression. Leukemia-free survival (LFS) was defined as a lifetime with continuous complete remission (CR). The event of overall survival (OS) was the death of any cause.

2.7 Statistical Analysis

The χ² and Fisher’s exact tests were used to compare categorical variables. The Mann–Whitney U test was used to compare continuous variables. The cumulative incidences of relapse, NRM, and GVHD were calculated using competing risk analyses (40). The probabilities for the IFN-α and DLI groups.

3 RESULTS

3.1 Patient Characteristics

Patient characteristics are shown in Table 1, Figure 2, and Supplemental Table S1. In particular, six HID HSCT recipients received ATG and low-dose PTCY for GVHD prophylaxis. A total of 51, 37, and 16 patients showed low-level, intermediate-level, and high-level RUNX1-RUNX1T1, respectively, after allo-HSCT. We observed that donor type, Kit mutation, other karyotypic abnormalities, and duration of immunosuppressive therapy before MRD were not associated with posttransplant RUNX1-RUNX1T1 levels (Supplementary Tables S2, S3 and Supplementary Figure S1); however, pre-transplant transcripts were associated with post-transplant RUNX1-RUNX1T1 levels (Supplementary Table S2 and Supplementary Figure S1C).

Eighty-eight patients received IFN-α as initial therapy. The median number of cycles of IFN-α therapy was 3 cycles (range, 1–26 cycles), and 24 of them received salvage DLI (chemo-DLI, 20; DLI alone, 4) after IFN-α therapy. Sixteen patients received DLI as initial therapy (chemo-DLI, 10; DLI alone, 6), and six of them received IFN-α as salvage therapy after DLI. The causes of NRM are infection, diffused alveolar hemorrhage, and GVHD (Supplementary Table S4). The cumulative incidences of relapse, NRM, LFS, and OS at 2 years after preemptive interventions were 16.8% [95% confidence interval (CI), 8.7%–24.8%] versus 19.6% (95% CI, 0.0%–40.5%) (p = 0.810), 3.6% (95% CI, 0.0%–7.7%) versus 20.1% (95% CI, 0.0%–41.3%) (p = 0.001), 78.2% (95% CI, 69.8%–87.7%) versus 60.3% (95% CI, 40.0%–90.9%) (p = 0.023), and 84.2% (95% CI, 76.6%–92.5%) versus 66.7% (95% CI, 46.6%–95.3%) (p = 0.004), respectively, for the IFN-α and DLI groups.
(Supplementary Table S5), and the duration from intervention to MRD turning negative was 25, 121, and 174 days, respectively. Three patients with persistent MRD positive received salvage IFN-α therapy after DLI, and all of them achieved MRD negative thereafter.

3.2.3 High-Level RUNX1-RUNX1T1 Before Immunotherapy

Nine patients received IFN-α therapy as initial therapy; two achieved MRD negative (22.2%, Supplementary Table S5), and the duration from intervention to MRD turning negative was 25, 121, and 174 days, respectively. Three patients with persistent MRD positive received salvage IFN-α therapy after DLI, and all of them achieved MRD negative thereafter.
negative was 23 and 48 days, respectively. Three patients with persistent MRD positive received salvage chemo-DLI after IFN-α therapy. Although two of them (66.7%) achieved a transient MRD negative after that, both experienced relapse.

Seven patients received chemo-DLI as initial therapy, 1 (14.3%) achieved MRD negative (Supplementary Table S5), and the duration from intervention to MRD turning negative was 68 days. Two patients with persistent MRD positive received salvage IFN-α therapy after chemo-DLI, and both achieved MRD-negative status afterward.

### 3.3 Chronic GVHD After Preemptive Immunotherapy

The cumulative incidence of total chronic GVHD (cGVHD) at 2 years after preemptive immunotherapy was 45.1% (95% CI, 32.4%–57.8%) in patients receiving IFN-α therapy alone, 57.1% (95% CI, 4.4%–100.0%) in patients receiving DLI alone, and 75.3% (95% CI, 58.6%–92.0%) in patients receiving both DLI and IFN-α therapy (p = 0.154). The cumulative incidence of severe cGVHD at 2 years after preemptive immunotherapy was 3.2% (95% CI, 0.0%–7.5%) in patients receiving IFN-α therapy alone, 0.0% in patients receiving DLI alone, and 10.1% (95% CI, 0.0%–21.2%) in patients receiving both DLI and IFN-α therapy (p = 0.288).

### 3.4 Relapse, NRM, and Survival After Preemptive Immunotherapy

#### 3.4.1 FAS

For patients with low-level and intermediate-level RUNX1-RUNX1T1 (i.e., 2.5–4.5-log reduction), the 2-year cumulative incidence of relapse after the intervention was comparable between the IFN-α and DLI groups, but the IFN-α group showed a lower cumulative incidence of NRM (Table 2). The probability of survival at 2 years in the IFN-α group was also significantly better than that of the DLI group (Table 2 and Figures 3A, B). Particularly, for patients with low levels of RUNX1-RUNX1T1, the cumulative incidence of relapse, NRM, LFS, and OS at 2 years after IFN-α therapy was 11.3% (95% CI, 1.8%–20.7%; 2.1% (95% CI, 0.0%–6.3%), 56.6% (95% CI, 77.1%–97.2%), and 88.8% (95% CI, 79.8%–98.6%), respectively.

For patients with high-level RUNX1-RUNX1T1 (i.e., <2.5-log reduction), the probabilities of survival at 2 years after intervention were all comparable between the IFN-α and DLI groups (Table 2 and Figures 3C, D).

In multivariate analysis, for patients receiving preemptive IFN-α therapy, the relapse and survival of the low-level and intermediate-level RUNX1-RUNX1T1 groups were superior to those of the high-level group (Table 3). In addition, identical sibling donors also predicted a high risk of relapse and poorer survival.

### Table 2 | The 2-year cumulative incidence of relapse, NRM, LFS, and OS after preemptive interventions.

| Low- and intermediate-level RUNX1-RUNX1T1* | n | Cumulative incidence (95% CI) | n | Cumulative incidence (95% CI) | p-value |
|-------------------------------------------|---|-----------------------------|---|-----------------------------|---------|
| Full analysis set                         | 79 | 12.2% (4.7%–19.8%)          | 9  | 11.1% (0%–33.3%)           | 0.870   |
| Relapse                                  | 11 | 4.1% (0%–8.6%)              | 1  | 33.3% (0.1%–66.5%)         | 0.001   |
| NRM                                      | 3  | 83.7% (75.7%–92.6%)         | 3  | 55.6% (31.0%–99.7%)        | 0.023   |
| LFS                                      | 65 | 87.6% (80.3%–95.6%)         | 5  | 55.6% (31.0%–99.7%)        | 0.003   |
| OS                                       | 69 | 83.7% (75.7%–92.6%)         | 5  | 20.0% (0.0%–60.4%)         | 0.203   |
| Per protocol set                         | 58 | 5.4% (0.0%–11.3%)           | 5  | 20.0% (0.0%–59.2%)         | 0.022   |
| Relapse                                  | 3  | 5.6% (0.0%–11.8%)           | 3  | 60.0% (29.3%–100.0%)       | 0.030   |
| NRM                                      | 3  | 89.1% (81.1%–97.7%)         | 3  | 60.0% (29.3%–100.0%)       | 0.017   |
| LFS                                      | 52 | 90.8% (83.5%–98.8%)         |      |                            |         |
| OS                                       | 53 |                            |      |                            |         |

*High-level, intermediate-level, and low-level MRDs were respectively defined as <2.5-log, 2.5- to 3.5-log, and 3.5- to 4.5-log reductions in the RUNX1-RUNX1T1 transcripts when compared with the pretreatment baseline level.

The full analysis set included all participants who received IFN-α or DLI as initial treatments at the time of MRD positive and those who received both IFN-α and DLI were included. The per-protocol set analysis included the patients who received IFN-α or DLI alone, and those who received both IFN-α and DLI were excluded.
3.4.2 PPS Analysis

In this analysis, patients who received both DLI and IFN-α treatment were excluded, and 64 and 10 patients in the IFN-α and DLI groups, respectively (Table 2).

For patients with low-level and intermediate-level RUNX1-RUNX1T1, the IFN-α group also showed significantly better OS and LFS rates than those of the DLI group (Table 2 and Figures 4A, B). Particularly, for patients with low-level RUNX1-RUNX1T1, the incidence of NRM, relapse, LFS, and OS at 2 years after IFN-α therapy was 5.2% (95% CI, 0.0%−12.3%), 2.6% (95% CI, 0.0%−7.6%), 92.2% (95% CI, 84.2%−100.0%), and 92.2% (95% CI, 84.2%−100.0%), respectively.

For patients with high-level RUNX1-RUNX1T1, the probability of survival at 2 years after the intervention was comparable between the IFN-α and DLI groups (Table 2 and Figures 4C, D).

In multivariate analysis, for patients receiving preemptive IFN-α treatment, the OS of the low-level and intermediate-level RUNX1-RUNX1T1 group was superior to that of the high-level group (Supplementary Table S6). Furthermore, identical sibling donors predicted poorer survival.

3.4.3 Analysis of Patients Who Received Both IFN-α and Chemo-DLI

A total of 30 patients receiving both IFN-α and DLI were included in this analysis (DLI followed by IFN, n = 6; IFN followed by DLI, n = 24; Figure 1).

For patients with low-level and intermediate-level RUNX1-RUNX1T1, the cumulative incidence of NRM at 2 years was lower in IFN-α followed by DLI group (0% vs. 50.0%, 95% CI, 0.0%−100.0%; p = 0.001) than those in DLI followed by the IFN-α group, but the probability of relapse and survival were all comparable between the groups (Supplementary Table S7).

Three patients with high-level RUNX1-RUNX1T1 received salvage DLI after IFN-α therapy. Two of them achieved MRD negative, but one of them experienced relapse and died. The patient with persistent MRD positive also experienced a relapse.

Two patients received salvage IFN-α after DLI, one of whom achieved MRD negative but died from pneumonia, and the other achieved MRD negative and persistent LFS until the last follow-up.

4 DISCUSSION

This study showed that patients with low-level and intermediate-level RUNX1-RUNX1T1 could benefit from preemptive IFN-α therapy. The clinical outcomes of preemptive IFN-α therapy and DLI in patients with high-level RUNX1-RUNX1T1 were unsatisfactory. To our knowledge, this is the first study to compare the efficacy of preemptive IFN-α therapy and DLI in a population of patients with a specific disease [i.e., t(8;21) AML] following allo-HSCT.
**TABLE 3** | Multivariate analysis of risk factors for the 2-year clinical outcomes after preemptive IFN-α therapy in full analysis set.

| Outcome                          | HR (95% CI) | p-value |
|----------------------------------|-------------|---------|
| **Relapse**                      |             |         |
| Disease status prior to allo-HSCT|             |         |
| CR1                              | 1           |         |
| >CR1                             | 3.02 (1.07–8.48) | 0.036  |
| MRD level before IFN-α therapy*  |             |         |
| High-level                       | 1           |         |
| Intermediate-level               | 0.18 (0.05–0.65) | 0.009  |
| Low-level                        | 0.16 (0.05–0.53) | 0.003  |
| **Donor type**                   |             |         |
| Alternative donor                | 1           |         |
| HLA-identical donor              | 6.04 (2.18–16.72) | 0.001  |
| **Treatment failure as defined by OS** |         |         |
| MRD level before IFN-α therapy*  |             |         |
| High-level                       | 1           |         |
| Intermediate-level               | 0.23 (0.06–0.89) | 0.034  |
| Low-level                        | 0.18 (0.05–0.67) | 0.011  |
| **Donor type**                   |             |         |
| Alternative donor                | 1           |         |
| HLA-identical donor              | 8.49 (2.77–26.01) | <0.001 |
| **Treatment failure as defined by LFS** |         |         |
| MRD level before IFN-α therapy*  |             |         |
| High-level                       | 1           |         |
| Intermediate-level               | 0.25 (0.08–0.81) | 0.021  |
| Low-level                        | 0.18 (0.06–0.59) | 0.004  |
| **Donor type**                   |             |         |
| Alternative donor                | 1           |         |
| HLA-identical donor              | 6.09 (2.41–15.40) | <0.001 |

*–HLA-identical donor, human leukocyte antigen; CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio; IFN, interferon; LFS, leukemia-free survival; MRD, minimal residual disease; OS, overall survival. 

We observed that the relapse rate was nearly one-third (27.4%) even in patients with low-level RUNXI-RUNXIT1 after transplantation (Qin et al., data unpublished) if no preemptive interventions were administered. In patients with low-level and intermediate-level RUNXI-RUNXIT1, most of them achieved MRD negative after IFN-α therapy. The rate of relapse was low, and the rate of survival was >80%, particularly for those with low-level RUNXI-RUNXIT1. In our previous study, the relapse and survival rates were 8% and 75%, respectively, for patients who were negative for RUNXI-RUNXIT1 in the first 3 months after allo-HSCT (14). Therefore, with the help of preemptive IFN-α therapy, patients with low-level and intermediate-level RUNXI-RUNXIT1 achieved comparable outcomes with those with persistent MRD-negative status after allo-HSCT. Patients with low-level and intermediate-level RUNXI-RUNXIT1 have been suggested to benefit more from preemptive IFN-α therapy, which could preferably be started in patients with a relatively low tumor burden (48).

In patients with high-level RUNXI-RUNXIT1, neither preemptive DLI nor IFN-α showed satisfactory outcomes. The survival of the IFN-α and DLI groups was comparable due to the small sample size of the DLI recipients. Furthermore, patients with high-level RUNXI-RUNXIT1 who showed an unsatisfactory response to DLI achieved MRD negative after salvage IFN-α treatment; however, those who showed an unsatisfactory response to IFN-α did not benefit from salvage DLI. We also observed that IFN-α salvage treatment was effective for patients who did not respond satisfactorily to preemptive DLI (18, 49). The number of patients who received both IFN-α and DLI was too small to draw any conclusions in this study, but this was an interesting phenomenon that suggested that therapeutic order may influence the outcomes of preemptive immunotherapy, and it is worth identifying in the future. Meanwhile, many new drugs (e.g., BCL-2 inhibitor) could be used in the treatment of AML, which would help to further improve the clinical outcomes of patients with high-level RUNXI-RUNXIT1 (50–52).

This was not a randomized trial, which was a limitation of the present study. Many patients might be inclined to choose IFN-α therapy because it can be conveniently performed in an outpatient setting, particularly for those with low-level and intermediate-level RUNXI-RUNXIT1. Therefore, it was too early to draw strong conclusions that DLI was inferior to IFN-α therapy in these patients, which should be confirmed by a randomized trial. Secondly, the number of patients with high-level RUNXI-RUNXIT1 was small. Because most of the patients with low-level and intermediate-level RUNXI-RUNXIT1 could clear the MRD after IFN-α therapy, the evolution of MRD was stopped in the early stage and did not develop into high-level RUNXI-RUNXIT1. Thus, the efficacy of DLI and IFN-α therapy in patients with high level of RUNXI-RUNXIT1 should also be further investigated.

**CONCLUSION**

This study showed that patients with low-level and intermediate-level RUNXI-RUNXIT1 could benefit more from preemptive...
IFN-α therapy compared with DLI. Clinical outcomes were comparable between preemptive IFN-α therapy and DLI in patients with high-level RUNX1-RUNX1T1; however, they should be further improved. In the future, randomized trials will compare the efficacy of IFN-α therapy with that of DLI in these patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

X-DM and X-JH designed the study. M-ZS, SF, X-HZ, L-PX, YW, C-HY, HC, Y-HC, WH, F-RW, J-ZW, X-SZ, Y-JC, and K-YL collected the data. M-ZS, SF, X-DM, and X-JH analyzed the data and drafted the manuscript. All authors contributed to the data interpretation, manuscript preparation, and approval of the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.773394/full#supplementary-material
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