A risk-stratified therapy for infants with acute lymphoblastic leukemia: a report from the JPLSG MLL-10 trial

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Table S1. A modified Eastern Cooperative Oncology Group (ECOG) performance status (PS) scoring system by the JPLSG Infant Leukemia Committee

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
</table>
| 0     | Fully active, good limb movement without restriction  
Normal suckling and dietary intake  
Crying strong; laughing in a good mood after solving a problem |
| 1     | Hypoactive, although with no restriction in limb movement  
Dietary intake reduced to 70% or less than usual  
Crying less strong; often laughing glumly |
| 2     | Quiet, reduced limb movements  
Dietary intake reduced to 50% or less than usual  
Crying weak; reduced laughing |
| 3     | Not doing well, seldom moves limbs  
Decreased appetite; dietary intake reduced to 25% or less than usual  
Crying rather weak; almost no laughing |
| 4     | Total absence of movement  
Unable to eat or drink  
Completely inactive; unable to cry; general apathy |
Table S2. Treatment protocol for patients with KMT2A-germline ALL (Regimen A)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose</th>
<th>Days of application per element</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction A (week 1-5)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone (PO/NG)</td>
<td>60 mg/m² per day</td>
<td>1-7, 22-35&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>10 mg/m² per day</td>
<td>8-21</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>8, 15, 22, 29</td>
</tr>
<tr>
<td>Cytarabine (IV over 1 hour)</td>
<td>1,200 mg/m² per dose</td>
<td>9</td>
</tr>
<tr>
<td>Doxorubicin (IV over 1 hour)</td>
<td>25 mg/m² per dose</td>
<td>10, 12</td>
</tr>
<tr>
<td>L-asparaginase (IV over 4 hours)</td>
<td>10,000 U/m² per dose</td>
<td>22, 24, 26, 29, 31, 33</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8, 22 (&amp; 15, 29, if CNS-3)</td>
</tr>
<tr>
<td><strong>Early Consolidation A (week 9-13)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide (IV over 2 hours)</td>
<td>100 mg/m² per dose</td>
<td>1-4</td>
</tr>
<tr>
<td>Cytarabine (IV over 4 hours)</td>
<td>500 mg/m² per dose</td>
<td>1-4</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td><strong>Consolidation A-I (week 9-13)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (IV over 24 hours)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3,000 mg/m² per dose</td>
<td>1, 15, 29</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1, 15, 29</td>
</tr>
<tr>
<td>Prednisolone (PO/NG)</td>
<td>60 mg/m² per day</td>
<td>1-3, 15-17, 29-31</td>
</tr>
<tr>
<td>Cytarabine (IV over 1 hour)</td>
<td>500 mg/m² per dose</td>
<td>3, 17, 31</td>
</tr>
<tr>
<td>L-asparaginase (IV over 4 hours)</td>
<td>10,000 U/m² per dose</td>
<td>3, 17, 31</td>
</tr>
<tr>
<td><strong>Consolidation A-II (week 15-17)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>1, 8, 15</td>
</tr>
<tr>
<td>Daunorubicin (IV over 1 hour)</td>
<td>25 mg/m² per dose</td>
<td>1, 8, 15</td>
</tr>
<tr>
<td>Cytarabine (IV over 1 hour)</td>
<td>60 mg/m² per dose</td>
<td>2-7, 9-14</td>
</tr>
<tr>
<td>6-mercaptopurine (PO/NG)</td>
<td>75 mg/m² per day</td>
<td>1-14</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1, 15</td>
</tr>
<tr>
<td><strong>Re-induction A (week 19-23)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>10 mg/m² per day</td>
<td>1-14</td>
</tr>
<tr>
<td>Prednisolone (PO/NG)</td>
<td>60 mg/m² per day</td>
<td>15-28&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>1, 8, 15, 22</td>
</tr>
<tr>
<td>Cyclophosphamide (IV over 1 hour)</td>
<td>1,200 mg/m² per dose</td>
<td>2</td>
</tr>
<tr>
<td>Doxorubicin (IV over 1 hour)</td>
<td>25 mg/m² per dose</td>
<td>3, 5</td>
</tr>
<tr>
<td>L-asparaginase (IV over 4 hours)</td>
<td>10,000 U/m² per dose</td>
<td>15, 17, 19, 22, 24, 26</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1, 15, 29</td>
</tr>
<tr>
<td>Etoposide (IV over 2 hours)</td>
<td>100 mg/m² per dose</td>
<td>29-32</td>
</tr>
<tr>
<td>Cytarabine (IV over 4 hours)</td>
<td>500 mg/m² per dose</td>
<td>29-32</td>
</tr>
<tr>
<td><strong>Maintenance A: Cycle #1 (week 26-39), #2 (week 40-53), #3 (week 54-67), #4 (week 68-80)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-mercaptopurine (PO/NG)</td>
<td>75 mg/m² per day</td>
<td>1-14, 29-42, 57-70</td>
</tr>
<tr>
<td>Methotrexate (PO/NG)</td>
<td>30 mg/m² per dose</td>
<td>1, 8, 29, 36, 57, 64</td>
</tr>
<tr>
<td>Etoposide (IV over 2 hours)</td>
<td>150 mg/m² per dose</td>
<td>14, 42</td>
</tr>
<tr>
<td>Cytarabine (IV over 4 hours)</td>
<td>200 mg/m² per dose</td>
<td>14, 42</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1, 29</td>
</tr>
<tr>
<td>Prednisolone (PO/NG)</td>
<td>60 mg/m² per day</td>
<td>71-84</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>71, 78, 85</td>
</tr>
<tr>
<td>Methotrexate (IV over 5 hours)</td>
<td>300 mg/m² per dose</td>
<td>71</td>
</tr>
</tbody>
</table>

PO, orally; NG, via nasogastric tube; IV, intravenous infusion; IT, intrathecally.

<sup>a</sup>Doses of each drug (except vincristine, prednisolone, and dexamethasone) were reduced by one-third in patients younger than 2 months and by one-fourth in those 2 to 4 months of age.

<sup>b</sup>Adjustments of time schedule were allowed if clinical condition and bone marrow recovery were inadequate.

<sup>c</sup>Leucovorin rescue was given at hours 42, 48, and 54 (each 15 mg/m²). Increased and/or extended leucovorin doses were given, when methotrexate (MTX) levels at hours 48, 72, and 96 were high until MTX levels were <0.2 μmol/L.

<sup>d</sup>Doses were adjusted according to the patient’s age at administration, as follows: <3 months old, MTX 3 mg, hydrocortisone (HDC) 10 mg, cytarabine (Ara-C) 6 mg; <1 year old, MTX 6 mg, HDC 10 mg, Ara-C 15 mg; <2 years old, MTX 8 mg, HDC 15 mg, Ara-C 20 mg; <3 years old, MTX 10 mg, HDC 20 mg, Ara-C 25 mg; ≥3 years old, MTX 12 mg, HDC 25 mg, Ara-C 30 mg.

<sup>e</sup>Prednisolone was tapered over 7 days.
Dexamethasone was tapered over 7 days.

Doses were adjusted according to the patient’s age at administration as follows: <6 months old, 1.7 mg/kg; <9 months old, 2.1 mg/kg; <3 months old, MTX 3 mg, hydrocortisone (HDC) 10 mg, cytarabine (Ara-C) 6 mg; <1 year old, MTX 8 mg, HDC 15 mg, Ara-C 20 mg; <2 years old, MTX 8 mg, HDC 20 mg, Ara-C 25 mg; <3 years old, MTX 10 mg, HDC 25 mg, Ara-C 30 mg.

Induction B (week 1-5)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone (PO/NG)</td>
<td>60 mg/m² per day</td>
<td>1-7</td>
</tr>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>6 mg/m² per day</td>
<td>8-28g</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>8, 15, 22, 29</td>
</tr>
<tr>
<td>Cytarabine (IV over 0.5 hour)</td>
<td>75 mg/m² per dose</td>
<td>8-21</td>
</tr>
<tr>
<td>Daunorubicin (IV over 1 hour)</td>
<td>30 mg/m² per dose</td>
<td>8, 9</td>
</tr>
<tr>
<td>L-asparaginase (IV over 1 hour)</td>
<td>10,000 U/m² per dose</td>
<td>15, 18, 22, 25, 29, 32</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>8, 29 (22, if CNS-3)</td>
</tr>
<tr>
<td>Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>15</td>
</tr>
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</table>

Early Consolidation B (week 6-11)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (IV over 24 hours)</td>
<td>4,000 mg/m² per dose</td>
<td>1, 8</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>1, 8</td>
</tr>
<tr>
<td>Etoposide (IV over 2 hours)</td>
<td>100 mg/m² per dose</td>
<td>1-2</td>
</tr>
<tr>
<td>Cyclophosphamide (IV over 0.5 hour)</td>
<td>300 mg/m² per dose</td>
<td>15-19</td>
</tr>
<tr>
<td>Cytarabine (IV over 3 hours)</td>
<td>3,000 mg/m² per dose</td>
<td>29-31 (4 doses, 12-hour intervals)</td>
</tr>
<tr>
<td>L-asparaginase (IM)</td>
<td>6,000 U/m² per dose</td>
<td>31h</td>
</tr>
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</table>

Re-induction B (week 13-15)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>10 mg/m² per day</td>
<td>1-7, 15-21</td>
</tr>
<tr>
<td>Vincristine (IV)</td>
<td>0.05 mg/kg per dose</td>
<td>8, 15</td>
</tr>
<tr>
<td>Daunorubicin (PI over 0.5 hour)</td>
<td>Age adjustedf</td>
<td>1, 2</td>
</tr>
<tr>
<td>Cyclophosphamide (PI over 0.5 hour)</td>
<td>250 mg/m² per dose</td>
<td>3, 4 (4 doses, 12-hour intervals)</td>
</tr>
<tr>
<td>L-asparaginase (IM)</td>
<td>6,000 U/m² per dose</td>
<td>3, 5, 8, 10, 12, 15, 17, 19</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>1, 15</td>
</tr>
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Late Consolidation B (week 16-21)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (IV over 24 hours)</td>
<td>4,000 mg/m² per dose</td>
<td>1, 8</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>1</td>
</tr>
<tr>
<td>Etoposide (IV over 2 hours)</td>
<td>100 mg/m² per dose</td>
<td>15-19</td>
</tr>
<tr>
<td>Cyclophosphamide (IV over 0.5 hour)</td>
<td>300 mg/m² per dose</td>
<td>15-19</td>
</tr>
<tr>
<td>Cytarabine (IV over 3 hours)</td>
<td>3,000 mg/m² per dose</td>
<td>29-31 (4 doses, 12-hour intervals)</td>
</tr>
<tr>
<td>L-asparaginase (IM)</td>
<td>6,000 U/m² per dose</td>
<td>31h</td>
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</tbody>
</table>

Maintenance B-I: Cycle #1 (week 23-26), #3 (week 36-39), #5 (week 49-52)

<table>
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<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>6 mg/m² per day</td>
<td>1-5</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>1</td>
</tr>
<tr>
<td>6-mercaptopurine (PO/NG)</td>
<td>75 mg/m² per day</td>
<td>8-28</td>
</tr>
<tr>
<td>Methotrexate (IV push)</td>
<td>20 mg/m² per dose</td>
<td>8, 15, 22</td>
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</table>

Maintenance B-I: Cycle #2 (week 27-35), #4 (week 40-48)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>6 mg/m² per day</td>
<td>1-5</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate/Cytarabine/Hydrocortisone (IT)</td>
<td>Age adjustede</td>
<td>1</td>
</tr>
<tr>
<td>6-mercaptopurine (PO/NG)</td>
<td>75 mg/m² per day</td>
<td>8-21</td>
</tr>
<tr>
<td>Methotrexate (IV push)</td>
<td>20 mg/m² per dose</td>
<td>8, 15</td>
</tr>
<tr>
<td>Etoposide (IV over 2 hours)</td>
<td>100 mg/m² per dose</td>
<td>22-26</td>
</tr>
<tr>
<td>Cyclophosphamide (IV over 0.5 hour)</td>
<td>300 mg/m² per dose</td>
<td>22-26</td>
</tr>
<tr>
<td>Cytarabine (IV over 3 hours)</td>
<td>3,000 mg/m² per dose</td>
<td>43-45 (4 doses, 12-hour intervals)</td>
</tr>
<tr>
<td>L-asparaginase (IM)</td>
<td>6,000 U/m² per dose</td>
<td>45h</td>
</tr>
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</table>

Maintenance B-II: Cycle #1 (week 53-64), #2 (week 65-76), #3 (week 77-88), #4 (week 89-100), #5 (week 101-112)

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose*</th>
<th>Days of application per elementb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (PO/NG)</td>
<td>6 mg/m² per day</td>
<td>1-5, 29-33, 57-61</td>
</tr>
<tr>
<td>Vincristine (IV push)</td>
<td>0.05 mg/kg per dose</td>
<td>1, 29, 57</td>
</tr>
<tr>
<td>Methotrexate (IT)</td>
<td>15 mg/m² per day</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate (PO/NG)</td>
<td>20 mg/m² per dose</td>
<td>8, 15, 22, 36, 43, 50, 64, 71, 78</td>
</tr>
</tbody>
</table>

**PO, orally; NG, via nasogastric tube; IV, intravenous infusion; IT, intrathecally, IM, intramuscularly.**

*a* Doses of each drug (except vincristine, prednisolone, and dexamethasone) were reduced by one-third in patients younger than 2 months and by one-fourth in those 2 to 4 months of age.

*b* Adjustments of time schedule were allowed if clinical condition and bone marrow recovery were inadequate.

*c* Loading dose of 10% was infused over 30 minutes, the remaining 90% over 23.5 hours. Leucovorin rescue was given at hours 42, 48, and 54 (each 15 mg/m²). Increased and/or extended leucovorin doses were given when methotrexate (MTX) levels at hours 48, 72, and 96 were high until MTX levels were <0.2 µmol/L.

*d* High-dose cytarabine and L-asparaginase was added to the original COG AALL0631 chemotherapy.

*e* Doses were adjusted according to the patient’s age at administration as follows: <3 months old, MTX 3 mg, hydrocortisone (HDC) 10 mg, cytarabine (Ara-C) 6 mg; <1 year old, MTX 6 mg, HDC 10 mg, Ara-C 15 mg; <2 years old, MTX 8 mg, HDC 15 mg, Ara-C 20 mg; <3 years old, MTX 10 mg, HDC 20 mg, Ara-C 25 mg; <3 years old, MTX 12 mg, HDC 25 mg, Ara-C 30 mg.

*f* Doses were adjusted according to the patient’s age at administration as follows: <6 months old, 1.7 mg/kg; <9 months old, 2.1 mg/kg; ≥9 months old, 2.6 mg/kg.

*g* Dexamethasone was tapered over 7 days.

*h* L-asparaginase was administered 3 hours after the completion of the last Ara-C infusion.

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**Table S3. Treatment protocol for patients with KMT2A-rearranged ALL (Regimen B)**
Table S4. Conditioning regimen of hematopoietic stem cell transplantation for patients with high-risk KMT2A-rearranged ALL

<table>
<thead>
<tr>
<th>Treatment element / drug</th>
<th>Single or daily dose</th>
<th>Days of application per element</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan (IV over 2 hours)</td>
<td>Determined by PK test&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–8, –7, –6, –5 (16 doses, 6-hour interval)</td>
</tr>
<tr>
<td>Etoposide (IV over 12 hours)</td>
<td>60 mg/kg per dose</td>
<td>–4</td>
</tr>
<tr>
<td>Cyclophosphamide (IV over 2 hours)</td>
<td>60 mg/kg per dose</td>
<td>–3, –2</td>
</tr>
<tr>
<td>Stem cell transplantation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*IV, intravenous infusion; PK, pharmacokinetic.

<sup>a</sup>Selection of a donor was left to each physician; however, either human leukocyte antigen (HLA) ≥4/6 serologically matched unrelated cord blood or HLA ≥5/6 matched related donor was recommended.

<sup>b</sup>Busulfan PK test was performed one week prior to the start of conditioning, as follows: after busulfan 0.6 mg/kg (IV over 2 hours) was administered, peripheral blood was sampled at 4 different points (before and 3, 6, and 8 hours after the busulfan administration) and plasma busulfan concentrations were centrally measured. The initial busulfan dose was recommended to target within 600-900 ng/mL of steady state concentration (Css).
**Table S5. Antibodies used for flow cytometric MRD detection.** Flow cytometric MRD (FCM-MRD) was measured using 4-color flow cytometry. Antibodies to determine MRD level by flow cytometry were purchased from Beckmann-Coulter (Brea, CA, USA), BD Bioscience (San Jose, CA, USA), and Miltenyi Biotec (Bergisch Gladbach, North Rhine-Westphalia, Germany). For flow cytometric analysis, bone marrow mononucleated cells were incubated with the antibodies for 15 minutes at room temperature in the dark, then red blood cells were lysed with FACS™ lysing solution (BD Bioscience) and washed once with Dulbecco's phosphate buffered saline purchased from Sigma-Aldrich (St. Louis, MO, USA). Data acquisition and analysis were performed with the FACSCalibur™ flow cytometer and CellQuest™ software (BD Biosciences). Viable nucleated cells (up to 1,000,000) were analyzed in each sample.

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Clone</th>
<th>Fluorochrome</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD38</td>
<td>T16</td>
<td>FTIC</td>
<td>Beckmann-Coulter</td>
</tr>
<tr>
<td>CD45</td>
<td>2D1</td>
<td>FTIC</td>
<td>BD Bioscience</td>
</tr>
<tr>
<td>CD58</td>
<td>AICD58</td>
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<td>Beckmann-Coulter</td>
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Table S6. Grade 3 and 4 adverse events by different treatment phases (Regimen A)

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<th>Cons A-II</th>
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<td>15 (100%)</td>
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Abbreviations: ANC, absolute neutrophil count; CNS, central nervous system; Cons, consolidation; Ind, induction; Maint, maintenance; SIADH, syndrome of inappropriate antidiuretic hormone secretion; WBC, white blood cells
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<td>74 (99%)</td>
<td>68 (91%)</td>
<td>64 (100%)</td>
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<td>69 (92%)</td>
<td>64 (100%)</td>
<td>16 (100%)</td>
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<td>68 (91%)</td>
<td>56 (88%)</td>
<td>15 (94%)</td>
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<tr>
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Abbreviations: ANC, absolute neutrophil count; CNS, central nervous system; Cons, consolidation; Ind, induction; SIADH, syndrome of inappropriate antidiuretic hormone secretion; WBC, white blood cells
Table S7-2. Grade 3 and 4 adverse events by different treatment phases (Regimen B: maintenance phases)

<table>
<thead>
<tr>
<th>Toxocities</th>
<th>Maint B-I week 23-26</th>
<th>Maint B-I week 27-35</th>
<th>Maint B-I week 36-39</th>
<th>Maint B-I week 40-48</th>
<th>Maint B-I week 49-52</th>
<th>Maint B-II week 53-64</th>
<th>Maint B-II week 65-76</th>
<th>Maint B-II week 77-88</th>
<th>Maint B-II week 89-100</th>
<th>Maint B-II week 101-112</th>
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<tbody>
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</tr>
<tr>
<td>Leukocytes (total WBC)</td>
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<td>13 (81%)</td>
<td>16 (100%)</td>
<td>9 (56%)</td>
<td>15 (94%)</td>
<td>16 (100%)</td>
<td>13 (81%)</td>
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<td>14 (88%)</td>
</tr>
<tr>
<td>Neutrophils/granulocytes</td>
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<td>16 (100%)</td>
<td>11 (69%)</td>
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<td>10 (63%)</td>
<td>15 (94%)</td>
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<td>13 (81%)</td>
<td>12 (75%)</td>
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<td>5 (31%)</td>
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<td>1 (6%)</td>
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</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; CNS, central nervous system; Maint, maintenance; SIADH, syndrome of inappropriate antidiuretic hormone secretion; WBC, white blood cells
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<th>Grade 5</th>
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<td>n = 38</td>
<td>n = 38</td>
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<tr>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage, CNS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage, pulmonary/upper respiratory</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhage/Bleeding-Other</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>21 (55%)</td>
<td>21 (55%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection with Grade 3-4 neutrophils</td>
<td>12 (32%)</td>
<td>12 (32%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection with normal ANC or Grade 1-2 neutrophils</td>
<td>10 (26%)</td>
<td>9 (24%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Infection with unknown ANC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; CNS, central nervous system; Cons, consolidation; Ind, induction; SIADH, syndrome of inappropriate antidiuretic hormone secretion; WBC, white blood cells
Figure S1. Treatment scheme of the MLL-10 study and MRD measurement timepoints

KMT2A-g (LR)

Induction A  | Early Consolidation A  | Consolidation A-I  | Consolidation A-II  | Re-Induction A  | Maintenance A
--- | --- | --- | --- | --- | ---
week 1 | 2 | 3 | 6 | 9 | 15 | 19 | 26 | 30
TP1 | TP2 | TP3 | TP4

KMT2A-r (IR/HR)

Induction B  | Early Consolidation B  | Re-induction B  | Late Consolidation B  | Maintenance B-I  | Maintenance B-II
--- | --- | --- | --- | --- | ---
week 1 | 2 | 3 | 6 | 13 | 16 | 23 | 53 | 112
TP1 | TP2 | TP3 | TP4

<table>
<thead>
<tr>
<th></th>
<th>TP1</th>
<th>TP2</th>
<th>TP3</th>
<th>TP4</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCM-MRD</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td>Ig/TCR PCR-MRD</td>
<td>X</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>KMT2A-fusion PCR-MRD</td>
<td>X</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

Figure S2. Event-free survival (A) and overall survival (B) according to the Interfant-06 risk group

A

![Event-free survival graph]

Probability of EFS (%) vs. Years from registration

P <0.001 (logrank)

Number at risk by year:

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interfant-LR</td>
<td>15</td>
<td>15</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Interfant-MR</td>
<td>42</td>
<td>33</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Interfant-HR</td>
<td>33</td>
<td>14</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

B

![Overall survival graph]

Probability of OS (%) vs. Years after registration

P =0.021 (logrank)

Number at risk by year:

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interfant-LR</td>
<td>15</td>
<td>15</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Interfant-MR</td>
<td>42</td>
<td>39</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Interfant-HR</td>
<td>33</td>
<td>25</td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>
Figure S3. Event-free survival by flow cytometric MRD (FCM-MRD) levels at different time points (KMT2A-r patients only) (A) TP1, day 15 of Induction B (negative, <0.01%; low, 0.01%<0.1%; high, \( \geq 0.1\% \)); (B) TP2, end of Induction B (negative, <0.01%; positive, \( \geq 0.01\% \)); (C) TP3, end of Early Consolidation B (negative, <0.01%; positive, \( \geq 0.01\% \))

![Graph A](image1)

\[ P = 0.036 \text{ (logrank)} \]

<table>
<thead>
<tr>
<th>Number at risk at year</th>
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<tbody>
<tr>
<td>negative</td>
</tr>
<tr>
<td>low</td>
</tr>
<tr>
<td>High</td>
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</table>

![Graph B](image2)

\[ P = 0.002 \text{ (logrank)} \]

<table>
<thead>
<tr>
<th>Number at risk at year</th>
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<tbody>
<tr>
<td>negative</td>
</tr>
<tr>
<td>positive</td>
</tr>
</tbody>
</table>

![Graph C](image3)

\[ P < 0.001 \text{ (logrank)} \]

<table>
<thead>
<tr>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
</tr>
<tr>
<td>positive</td>
</tr>
</tbody>
</table>

Figure S4. Event-free survival by Ig/TCR PCR-MRD levels at different time points (KMT2A-r patients only) (A) TP2, end of Induction B; (B) TP3, end of Early Consolidation B; (C) TP4, before starting Maintenance B or HSCT (negative, \(<5 \times 10^{-4}\); positive, \( \geq 5 \times 10^{-4}\))

![Graph A](image4)

\[ P = 0.300 \text{ (logrank)} \]

<table>
<thead>
<tr>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
</tr>
<tr>
<td>positive</td>
</tr>
</tbody>
</table>

![Graph B](image5)

\[ P < 0.001 \text{ (logrank)} \]

<table>
<thead>
<tr>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
</tr>
<tr>
<td>positive</td>
</tr>
</tbody>
</table>

![Graph C](image6)

\[ P < 0.001 \text{ (logrank)} \]

<table>
<thead>
<tr>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
</tr>
<tr>
<td>positive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
</tr>
</tbody>
</table>
Figure S5. Event-free survival by KMT2A-fusion PCR-MRD levels at different time points (KMT2A-r patients only) (A) TP2, end of Induction B; (B) TP3, end of Early Consolidation B (negative, <50 copies/μgRNA; positive, ≧50 copies/μgRNA)

Figure S6. Event-free survival by flow cytometric MRD (FCM-MRD) risk groups (KMT2A-r patients only)
Figure S7. Event-free survival (A) and overall survival (B) of consecutive “MLL” trial series.

![Graphs showing event-free survival and overall survival](image)

<table>
<thead>
<tr>
<th></th>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>MLL96</td>
<td>42</td>
</tr>
<tr>
<td>MLL98</td>
<td>38</td>
</tr>
<tr>
<td>MLL03</td>
<td>62</td>
</tr>
<tr>
<td>MLL-10</td>
<td>75</td>
</tr>
</tbody>
</table>

**A**  
P = 0.004 (logrank)

<table>
<thead>
<tr>
<th></th>
<th>Number at risk at year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>MLL96</td>
<td>42</td>
</tr>
<tr>
<td>MLL98</td>
<td>38</td>
</tr>
<tr>
<td>MLL03</td>
<td>62</td>
</tr>
<tr>
<td>MLL-10</td>
<td>75</td>
</tr>
</tbody>
</table>

**B**  
P < 0.001 (logrank)