Outstanding outcomes in infants with KMT2A-germline acute lymphoblastic leukemia treated with chemotherapy alone: results of the Children’s Oncology Group AALL0631 trial

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# SUPPLEMENTAL TABLES

Table S1 Treatment details for infants with KMT2A-g leukemia

| Route | Dose | Day(s) of phase |
|-------|------|----------------|
| **Cohort 2 Induction (5 weeks)** | | |
| Prednisone (or methylprednisolone IV at 80% of the prednisone dose) | PO div TID | Age ≥6 months, 45 mg/m²/day  <br> Age ≥7 days to <6 months, 40 mg/m²/day  <br> Age <7 days, 30 mg/m²/day | 1-7 |
| Dexamethasone | IV or PO div TID | Age ≥6 months, 4.5 mg/m²/day  <br> Age ≥7 days to <6 months, 4 mg/m²/day  <br> Age <7 days, 3 mg/m²/day | 8-28 |
| Vincristine | IV push | Age ≥6 months, 1.125 mg/m²  <br> Age ≥7 days to <6 months, 1 mg/m²  <br> Age <7 days, 0.75 mg/m² | 8, 15, 22, 29 |
| Daunorubicin | IV over 30 min | Age ≥6 months, 22.5 mg/m²  <br> Age ≥7 days to <6 months, 20 mg/m²  <br> Age <7 days, 15 mg/m² | 8, 9 |
| *E. coli* L-Asparaginase (or *Erwinia* L-asparaginase) | IM | Age ≥6 months, 7500 IU/m² (or *Erwinia*, 30,000 IU/m²)  <br> Age ≥7 days to <6 months, 6675 IU/m² (or *Erwinia*, 27,000 IU/m²)  <br> Age <7 days, 5000 IU/m² (or *Erwinia*, 20,000 IU/m²) | 15, 18, 22, 25, 29, 33 |
| Cytarabine | IV over 30 min | Age ≥6 months, 56.25 mg/m²  <br> Age ≥7 days to <6 months, 50 mg/m²  <br> Age <7 days, 37.5 mg/m² | 8-21 |
| Methotrexate (MTX) | IT | Age <1 year, 6 mg  <br> Age ≥1 year, 8 mg | 1, 29 |
| Cytarabine (ARAC) | IT | Age <1 year, 15 mg  <br> Age ≥1 year, 20 mg | 15 |
| Hydrocortisone (HC) | IT | Age <1 year, 12 mg  <br> Age ≥1 year, 16 mg | 15, 29 |
| **Induction Intensification (4 weeks)** | | |
| High dose methotrexate | IV over 24 hours | 4000 mg/m² | 1, 8 |
| Triple intrathecal therapy | IT | Age <1 year, MTX 7.5 mg, ARAC 15 mg, HC 7.5 mg  <br> Age ≥1 year, MTX 8 mg, ARAC 16 mg, HC 8 mg  <br> Delivered within 6 hours of start of IV methotrexate | 1, 8 |
| Agent                  | Route                        | Dosage                          | Notes                                      |
|------------------------|------------------------------|---------------------------------|--------------------------------------------|
| Leucovorin rescue      | IV or PO                     | 15 mg/m² at hours 42, 48 after start of IV methotrexate | 2, 9                                      |
| Etoposide              | IV over 2 hrs                | 100 mg/m²                        | 15-19                                      |
| Cyclophosphamide       | IV over 30 min               | 300 mg/m²                        | 15-19                                      |
| Mesna                  | IV over 30 min followed by CI| 150 mg/m² with cyclophosphamide and as a 4-hour continuous infusion following cyclophosphamide, 2 doses per day | 15-19                                      |
| Filgrastim             | SQ or IV                     | 5 mcg/kg/dose daily until ANC >1500/µL x 2 days post nadir | Beginning on day 20                      |
| **Re-Induction (3 weeks)** |                              |                                 |                                            |
| Vincristine            | IV push                      | 0.05 mg/kg                       | 1, 15, 8                                   |
| Daunorubicin           | IV over 30 min               | Age <6 months, 1.7 mg/kg         | 1, 2                                       |
|                       |                              | Age ≥6 to <9 months, 2.1 mg/kg   |                                            |
|                       |                              | Age ≥9 months, 2.6 mg/kg         |                                            |
| Cyclophosphamide       | IV over 30 min               | 250 mg/m² every 12 hours         | 3, 4                                       |
| Mesna                  | IV over 30 min followed by CI| 125 mg/m² with cyclophosphamide and as a 4-hour continuous infusion following cyclophosphamide, 4 doses per day | 3, 4                                       |
| Pegasparagase          | IM                           | 2500 IU/m²                       | 4                                          |
| Dexamethasone          | PO or IV                     | 5 mg/m²/dose BID                 | 1-7 and 15-21                             |
| Triple intrathecal therapy | IT                          | Age <1 year, MTX 7.5 mg, ARAC 15 mg, HC 7.5 mg | 1, 15                                      |
|                       |                              | Age ≥1 year, MTX 8 mg, ARAC 16 mg, HC 8 mg |                                            |
| Filgrastim             | SQ or IV                     | 5 mcg/kg daily until ANC >1500/µL x 2 days post nadir | Beginning on day 5                      |
| **Consolidation (7 weeks)** |                              |                                 |                                            |
| Repeat Days 1-19 of Induction Intensification |                              |                                 | 1-19                                      |
| Filgrastim             | SQ or IV                     | 5 mcg/kg/dose daily until ANC >1500/µL x 2 days post nadir | Beginning on days 20 and 31 |
| High dose cytarabine   | IV over 3 hrs                | 3000 mg/m² every 12 hours        | 29, 30                                    |
| Pegaspargase           | IM                           | 2500 IU/m² administered 3 hours after final high dose cytarabine | 30                                         |
| **Continuation I (2 cycles, 11 weeks each)** |                              |                                 |                                            |
| Vincristine            | IV push                      | 0.05 mg/kg                       | 1, 29                                      |
| Dexamethasone          | PO or IV                     | 3 mg/m²/dose BID                 | 1-5 and 29-33                             |
| Triple intrathecal therapy | IT                          | Age <1 year, MTX 7.5 mg, ARAC 15 mg, HC 7.5 mg | 1, 29                                      |
|                       |                              | Age ≥1 year, MTX 8 mg, ARAC 16 mg, HC 8 mg |                                            |
| Methotrexate           | IV push                      | 20 mg/m²                         | 8, 15, 22, 36, 43, 50                     |
| Mercaptopurine         | PO                           | 75 mg/m²                         | 8-28 and 36-56                            |
| Etoposide              | IV over 2 hrs                | 100 mg/m²                        | 57-61                                      |
| Cyclophosphamide       | IV over 30 min               | 300 mg/m²                        | 57-61                                      |
| Drug       | Route | Dose/Details                                                                 | Dates   |
|------------|-------|-----------------------------------------------------------------------------|---------|
| Mesna      | IV    | 150 mg/m² with cyclophosphamide and as a 4-hour continuous infusion following cyclophosphamide, 2 doses per day | 57-61   |
| Filgrastim | SQ or IV | 5 mcg/kg/dose daily until ANC >1500/µL x 2 days post nadir                     | Beginning on day 62 |
| Vincristine| IV push | 0.05 mg/kg                                                                  | 1, 29, 57 |
| Dexamethasone | PO or IV | 3 mg/m²/dose BID                                                             | 1-5, 29-33, 57-61 |
| Methotrexate | IT     |                              | 1       |
| Methotrexate | PO     | 20 mg/m²                                                                    | 8, 15, 22, 36, 43, 50, 64, 71, 78 |
| Mercaptopurine | PO     | 75 mg/m²                                                                    | 8-28, 36-56, 64-84 |

Abbreviations: KMT2A-g, KMT2A-germline; IV, intravenous; IT, intrathecal; MTX, methotrexate; ARAC, cytarabine; HC, hydrocortisone; PO, by mouth; div, divided; mg, milligram; TID, three times daily; min, minutes; IM, intramuscular; IU, international units; hrs, hours; CI, continuous infusion; SQ, subcutaneous; mcg, microgram; kg, kilogram; ANC, absolute neutrophil count; BID, twice daily
Table S2. Complete karyotypes for *KMT2A*-g cases with available cytogenetic data

| Patient | Age at diagnosis | Diagnosis | WBC count at diagnosis | Karyotype |
|---------|------------------|-----------|------------------------|-----------|
| 1       | 160 days         | B-ALL     | 94.9                   | 45,XY,dic(9;20)(p13;q11.2)[19]/46,XY[2] |
| 2       | 174 days         | B-ALL     | 2.4                    | 45,XX,dic(9;17)(p13;p11.2)[5]/46,XX[10] |
| 3       | 200 days         | B-ALL     | 2.8                    | 46,XY,add(7)(p13),der(9)t(9;10)(p13;p13),der(9)t(9;10)(p13;q24),der(10)t(9;10)(p13;p13)t(9;10)(p13;q24)[14]/46,XY[6] |
| 4       | 268 days         | B-ALL     | 212.3                  | 46,XY,add(9)(p22),-11,der(11)t(9;11)(p13;p11.2)ins(11;?)(p11.2;?),+del(15)(q22q24),der(15)(15pter->15q24::11q23->11q13::9p22->9pter)[17]/46,XY[3] |
| 5       | 299 days         | B-ALL     | 21.6                   | 45,XY,dic(9;20)(p13;q11.2)[13]/46,XY[7] |
| 6       | 322 days         | B-ALL     | 143.5                  | 46,XY,r(4)(p16q35),del(9)(p13),rea(12)[7]/46,XY[16] |
| 7       | 331 days         | B-ALL     | 14.5                   | 46,XX,t(1;7)(q21;p22),dic(9;20)(p13;q11.2),+21[15]/46,sl,del(6)(q11.2q22.31)[2]/46,XX[2] |
| 8       | 331 days         | B-ALL     | 89.9                   | 45,XX,dic(9;20)(p13;q11.2)[4]/46,XX[36] |
| 9       | 333 days         | B-ALL     | 520.4                  | 45,XX,dic(9;20)(p13;q11.2)[20] |
| 10      | 349 days         | B-ALL     | 140                    | 46,X,t(X;7;9;1)(q22;q22;q24;p13)[17]/46,XX[3] |
|         |                   |           |                        | t(1;19)(q23;p13.3) or 19p13 variant |
| 11      | 252 days         | B-ALL     | 51                     | 46,XX,t(1;19)(q23;p13.3)[9]/46,XX[16] |
| 12      | 307 days         | B-ALL     | 68.9                   | 46,XX,der(19)t(1;19)(q23;p13.3)[4]/46,XX[16] |
| 13      | 308 days         | B-ALL     | 10.2                   | 46,XX,add(19)(p13.3)[8]/46,XX[11] |
| No. | Days  | Status | Time  | Chromosome Details |
|-----|-------|--------|-------|--------------------|
| 14  | 338   | B-ALL  | 134.7 | 47,XX,t(1;19)(q23;p13.3),+6[cp6]/46,XX[14] |
| 15  | 363   | B-ALL  | 58.3  | 46,XY,der(19)t(1;19)(q23;p13)[7]/46,XY[13] |
|     |       |        |       | Hyperdiploid (>51 chromosomes) |
| 16  | 292   | B-ALL  | 38.8  | 55,XX,+X,+4,+6,+8,+14,+17,+18,+21,+21[16]/46,XX[6] |
| 17  | 313   | B-ALL  | 168   | 54,XY,+X,+Y,+4,+6,+17,+18,+18,+21[cp4]/46,XY[16] |
| 18  | 351   | B-ALL  | 6     | 53,XX,+X,+4,+6,+10,+18,+21,+21[2]/54,sl,+9[1]/54,sl,i(7)(q10),+9[6]/46,XX[11] |
| 19  | 322   | T-ALL  | 918.2 | 46,XY,t(6;7)(q23;q34)[14]/46,XY[6] |
| 20  | 360   | T-ALL  | 405.3 | 46,XX,t(7;14)(p13;q11.2),der(9)[9qter->9q13::9p13->9qter][15]/46,XX[5] |
|     |       |        |       | t(12;21)(p13;q22) or variant |
| 21  | 360   | B-ALL  | 67.8  | 46,XY,ins(21;12)(q22;p13p13)/47,sl,+mar[4]/46,XY |
|     |       |        |       | Abnormal, other |
| 22  | 54    | B-ALL  | 43    | 46,X,t(X;10;14)(p21.2;p12.2;q24)[16]/46,XX[30] |
| 23  | 128   | T-ALL  | 445.5 | 46,X,t(X;11)(q25;p13)[20] |
| 24  | 139   | B-ALL  | 27.5  | 46,XY,t(5;15)(p15.3;q13)[4]/46,XY[16] |
| 25  | 153   | B-ALL  | 25    | 46,XX,del(6)(q13q21)[5]/46,XX[15] |
| 26  | 199   | B-ALL  | 193.4 | 46,XX,i(1)(q10)[12]/46,XX[10] |
| 27  | 206   | B-ALL  | 43.9  | 46,XY,t(7;15)(q22;q15)[9]/46,XY[11] |
| 28  | 226   | B-ALL  | 103.8 | 46,XX,add(3)(q25),?dup(8)(q21.1q21.3),der(12)del(12)(p11.2p12)t(12;15)(q13;q22),der(15)t(12;15)[20] |
| No. | Days    | Type   | WBC   | Karyotype                                                                 |
|-----|---------|--------|-------|---------------------------------------------------------------------------|
| 29  | 250     | B-ALL  | 29.76 | 46,XY,t(2;7)(p11.2;p15)[11]/46,XY[9]                                      |
| 30  | 261     | B-ALL  | 9.8   | 46,XX,del(9)(q13q22),der(21)t(21;21)(p11.2;q22)[3]/46,XX[17]            |
| 31  | 277     | B-ALL  | 156.4 | 46,XX,i(8)(q10)[12]/47,XX,+8[4]/46,XX[4]                                |
| 32  | 282     | B-ALL  | 10.7  | 46,XX,t(5;15)(p15;q11.2)[10]/46,XX[10]                                  |
| 33  | 288     | B-ALL  | 229   | 45,XX,der(7;12)dic(7;12)(p11.1;p11.1)inv(12)(p13.3q24.3)[8]/46,XX[12]   |
| 34  | 309     | B-ALL  | 29.6  | 46,XY,t(3;15;8)(p12;q13;p11.2)[15]/46,XY[5]                             |
| 35  | 331     | B-ALL  | 10.6  | 47,XY,+10[17]/48,sl,+X[2]/46,XY[3]                                      |
| 36  | 363     | B-ALL  | 21    | 44,XX,del(3)(p21),-5,add(6)(p21.3),add(6)(p25),-7,add(8)(p23),del(13)(q14q22),add(14)(q21),-15,-19,+21,add(21;22)(p11.2;p11.2),+22,der(22)(14qter->14q21::??:22p11.2->22qter),+mar[cp3]/45,sl,+10[cp6]/46,XX[15] |
| 37  | 78      | B-ALL  | 78.9  | 46,XY[20]                                                                |
| 38  | 97      | B-ALL  | 84.8  | 46,XX[20]                                                                |
| 39  | 122     | B-ALL  | 29.7  | 46,XX[20]                                                                |
| 40  | 135     | B-ALL  | 2.6   | 46,XY[20]                                                                |
| 41  | 163     | B-ALL  | 10    | 46,XX[20]                                                                |
| 42  | 201     | B-ALL  | 11.6  | 46,XX[20]                                                                |
| 43  | 221     | B-ALL  | 29.7  | 46,XX[20]                                                                |
| 44  | 245     | B-ALL  | 15.8  | 46,XY[20]                                                                |
| 45  | 255     | B-ALL  | 5     | 46,XY[24]                                                                |
| 46  | 261     | T-ALL  | 24.6  | 46,XX[30]                                                                |
|   |   |   |   |   |
|---|---|---|---|---|
| 47 | 295 days | B-ALL | 620.1 | 46,XY[22] |
| 48 | 313 days | B-ALL | 0.6 | 46,XY[23] |
| 49 | 315 days | B-ALL | 9.9 | 46,XX[44] |
| 50 | 325 days | B-ALL | 10 | 46,XX[21] |
| 51 | 329 days | T-ALL | 620 | 46,XX[20] |
| 52 | 342 days | B-ALL | 32.9 | 46,XY[20] |
| 53 | 355 days | T-ALL | 375.2 | 46,XY[20] |

Abbreviations: *KMT2A*-g, *KMT2A-*germline; WBC, white blood cell; B-ALL, B-acute lymphoblastic leukemia; T-ALL, T-acute lymphoblastic leukemia; TRA, T cell Receptor Alpha; TRB, T cell Receptor Beta
Table S3. Grade 3 and 4 toxicities reported for infants with KMT2A-g leukemia

|                               | Induction | Induction Intensification | Reinduction | Consolidation | Continuation I | Continuation II | All Reporting Periods |
|-------------------------------|-----------|---------------------------|-------------|--------------|----------------|-----------------|-----------------------|
|                               | N=64      | N=60                      | N=60        | N=57         | N=56           | N=56           | N=64                  |
| Infectious                    |           |                           |             |              |                |                 |                       |
|                               | 21 (33%)  | 15 (25%)                  | 12 (20%)    | 22 (37%)     | 25 (44%)       | 23 (41%)       | 48 (75%)               |
| Gastrointestinal              |           |                           |             |              |                |                 |                       |
|                               | 15 (23%)  | 31 (52%)                  | 6 (10%)     | 18 (30%)     | 7 (12%)        | 4 (7%)         | 48 (75%)               |
| Metabolism/Nutrition          |           |                           |             |              |                |                 |                       |
|                               | 23 (36%)  | 20 (33%)                  | 13 (22%)    | 15 (25%)     | 11 (19%)       | 9 (16%)        | 39 (61%)               |
| Nervous                       |           |                           |             |              |                |                 |                       |
|                               | 1 (2%)    | --                        | --          | --           | 1 (2%)         | 2 (4%)         | 3 (5%)                 |
| Respiratory                   |           |                           |             |              |                |                 |                       |
|                               | 4 (6%)    | 4 (7%)                    | --          | 2 (3%)       | 3 (5%)         | 3 (5%)         | 11 (17%)               |
| Skin/Subcutaneous             |           |                           |             |              |                |                 |                       |
|                               | 6 (9%)    | 5 (8%)                    | 3 (5%)      | 4 (7%)       | --             | 1 (2%)         | 17 (27%)               |
| Cardiac                       |           |                           |             |              |                |                 |                       |
|                               | 1 (2%)    | 1 (2%)                    | --          | --           | 1 (2%)         | --             | 2 (3%)                 |
| Vascular                      |           |                           |             |              |                |                 |                       |
|                               | 9 (14%)   | 1 (2%)                    | 1 (2%)      | --           | 1 (2%)         | --             | 10 (16%)               |
| Hematologic                   |           |                           |             |              |                |                 |                       |
| Neutropenia                   |           |                           |             |              |                |                 |                       |
|                               | 18 (28%)  | 8 (13%)                   | 9 (15%)     | 10 (17%)     | 17 (30%)       | 8 (14%)        | 35 (55%)               |
| Thrombocytopenia              |           |                           |             |              |                |                 |                       |
|                               | 1 (2%)    | 1 (2%)                    | 2 (3%)      | 4 (7%)       | 3 (5%)         | 1 (2%)         | 10 (16%)               |

Abbreviations: KMT2A-g, KMT2A-germline