**Appendix**

**Molecular profiling defines distinct prognostic subgroups in childhood acute myeloid leukemia: a report from the French ELAM02 study group**

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[**Appendix Table S1:** Patients' characteristics at AML diagnosis. 3](#_Toc499821717)

[**Appendix Table S2:** Fusion transcripts identified by LD-RTPCR. 3](#_Toc499821718)

[**Appendix Table S3:** Patients’ characteristics according to complete remission status after two courses of intensive induction chemotherapy. 4](#_Toc499821719)

[**Appendix Table S4:** 3-years OS for molecular classifier subgroups. 5](#_Toc499821720)

[**Appendix Table S5:** 3-years OS according to the 2017 ELN risk stratification. 5](#_Toc499821721)

[**Appendix Figure S1:** Number of mutations according to age classes. 6](#_Toc499821722)

[**Appendix Figure S2:** Number of mutations according to cytogenetics. 6](#_Toc499821723)

[**Appendix Figure S3:** Genomic landscape of childhood AML according to age groups.. 7](#_Toc499821724)

[**Appendix Figure S4:** Childhood AML outcome according to cytogenetic subgroups. 8](#_Toc499821725)

[**Appendix Figure S5:** Childhood AML outcome according to gene mutations. 9](#_Toc499821726)

[**Appendix Figure S6:** Impact of *FLT3-ITD* status in childhood AML with poor molecular risk. 11](#_Toc499821727)

# Appendix Table S1: Patients' characteristics at AML diagnosis (total ELAM02 cohort vs. studied cohort).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | | | **No. (%)**  **ELAM02 study (n=438)** | **No. (%)**  **Present study (n=385)** |
| Sex | |  |  |  |
|  | Male | | 238 (54.3) | 210 (54.5) |
|  | Female | | 200 (45.7) | 175 (45.5) |
| Median age, years (range) | | | 8.2 (0-18) | 8.6 (0-18) |
| Median WBC count, x109/L (range) | | | 15.4 (0.40-575) | 16.6 (0.40-575) |
| Cytogenetics | | |  |  |
|  | CBF-rearranged | | 97 (22.1) | 92 (23.9) |
|  |  | inv(16)/t(16;16) | 36 (8.2) | 35 (9.1) |
|  |  | t(8;21) | 61 (13.9) | 57 (14.8) |
|  | *KMT2A* (*MLL*)-rearranged | | 95 (21.7) | 79 (20.5) |
|  |  | t(9;11) | 40 (9.1) | 36 (9.4) |
|  |  | no t(9;11) | 55 (12.6) | 43 (11.1) |
|  | Normal karyotype | | 109 (24.9) | 101 (26.2) |
|  | Others | | 77 (17.6) | 73 (19) |
|  | Adverse | | 55 (12.5) | 40 (10.4) |
|  |  | Complex karyotype | 39 (8.9) | 27 (7) |
|  |  | monosomy 7 | 11 (2.5) | 9 (2.3) |
|  |  | t(6;9) | 5 (1.1) | 4 (1) |
| Remission | | | 398 (90.9) | 350 (90.9) |
| EFS, 3 years | | | 56% (49.7-63.6) | 58.9% (54-63.9) |
| OS, 3 years | | | 71.5% (65-78) | 76.1% (71.8-80.4) |

# Appendix Table S2: Fusion transcripts identified by LD-RTPCR.

|  |  |  |
| --- | --- | --- |
| **Fusion transcripts** | **Corresponding cytogenetic aberration** | **Number of positive patients, n (%)** |
| *RUNX1-RUNX1T1* | t(8;21)(q22;q22) | 57 (14.8%) |
| *KMT2A-MLLT3* | t(9;11)(p22;q23) | 36 (9.4%) |
| *CBFB-MYH11* | inv(16)(p13q22) or t(16;16)(p13;q22) | 35 (9.1%) |
| *KMT2A-MLLT10* | t(10;11)(p12;q23) | 13 (3.4%) |
| *NUP98-NSD1* | t(5;11)(q35;p15.5) | 9 (2.3%) |
| *KMT2A-ELL* | t(11;19)(q23;p13.1) | 6 (1.6%) |
| *KMT2A-MLLT1* | t(11;19)(q23;p13.3) | 5 (1.3%) |
| *KMT2A-MLLT4* | t(6;11)(q27;q23) | 5 (1.3%) |
| *PICALM-MLLT10* | t(10;11)(p13;q21) | 5 (1.3%) |
| *DEK-NUP214* | t(6;9)(p22;q34) | 4 (1.0%) |
| *KMT2A-MLLT11* | t(1;11)(q21;q23) | 3 (0.8%) |
| *KMT2A-SEPT6* | t(X;11)(q24;q23)) | 2 (0.5%) |
| *KAT6A-CREBBP* | t(8;16)(p11;p13) | 1 (0.3%) |
| *KMT2A-ABI1* | t(10;11)(p12;q23) | 1 (0.3%) |
| *KMT2A-ADARB2* | t(10;11)(p15.3;q23) | 1 (0.3%) |
| *KMT2A-EPS15* | t(1;11)(p32;q23) | 1 (0.3%) |
| *KMT2A-KIAA1524* | t(3;11)(q13.3;q23) | 1 (0.3%) |
| *KMT2A-PICALM* | t(11;11)(q14;q23) | 1 (0.3%) |
| *KMT2A-SEPT5* | t(11;22)(q23;q11.2) | 1 (0.3%) |
| *MN1-ETV6* | t(12;22)(p13;q12) | 1 (0.3%) |
| *MYB-GATA1* | t(X;6)(p11;q23) | 1 (0.3%) |
| *NUP98-JARID1A* | t(11;12)(p15;p13) | 1 (0.3%) |
| *RBM15-MKL1* | t(1;22)(p13;q13) | 1 (0.3%) |

# Appendix Table S3: Patients’ characteristics according to complete remission status after two courses of intensive induction chemotherapy.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | |  | **Total No.** | **CR** | **no CR** | **p-value** |
| Sex (M/F) | |  | 210/175 | 187/163 | 23/12 | 0.164 |
| WBC>30**×**109/L | |  | 148 | 128 | 20 | 0.017\* |
| **Cytogenetics** | |  |  |  |  | 0.028\* |
|  | CBF |  | 92 | 88 | 4 | 0.094 |
|  | *KMT2A*-rearranged | | 79 | 76 | 3 | 0.079 |
|  | Normal |  | 101 | 90 | 11 | 0.545 |
|  | Others | | 73 | 61 | 12 | 0.023\* |
|  | Adverse |  | 40 | 35 | 5 | 0.389 |
| *NUP98* fusions | | | 10 | 5 | 5 | 0.001\* |
| **Gene mutations** | | |  |  |  |  |
| Tyrosine kinase pathway | | | 236 | 213 | 23 | 0.792 |
|  | *FLT3-ITD* |  | 57 | 46 | 11 | 0.004\* |
|  | *FLT3-TKD* |  | 33 | 31 | 2 | 0.754 |
|  | *KIT* |  | 48 | 46 | 2 | 0.286 |
|  | *NRAS* |  | 102 | 94 | 8 | 0.609 |
|  | *KRAS* |  | 47 | 42 | 5 | 0.598 |
|  | *CBL* |  | 1 | 1 | 0 | 1.000 |
|  | *PTPN11* |  | 24 | 22 | 2 | 1.000 |
|  | *JAK2* |  | 11 | 10 | 1 | 1.000 |
|  | *MPL* |  | 2 | 2 | 0 | 1.000 |
|  | *SETBP1* |  | 4 | 3 | 1 | 0.318 |
| Transcription Factors | | | 61 | 55 | 6 | 0.825 |
|  | *CEBPA* |  | 25 | 24 | 1 | 0.715 |
|  | *RUNX1* |  | 24 | 20 | 4 | 0.257 |
|  | *GATA2* |  | 16 | 16 | 0 | 0.380 |
|  | *GATA1* |  | 1 | 1 | 0 | 1.000 |
|  | *ETV6* |  | 7 | 6 | 1 | 0.490 |
| Epigenetic | |  | 58 | 54 | 4 | 0.629 |
| -Chromatin Modifiers | | | 33 | 33 | 0 | 0.058 |
|  | *ASXL1* |  | 9 | 9 | 0 | 1.000 |
|  | *EZH2* |  | 10 | 10 | 0 | 0.609 |
|  | *BCOR* |  | 5 | 5 | 0 | 1.000 |
|  | *BCORL1* |  | 6 | 6 | 0 | 1.000 |
| -DNA Methylation | | | 30 | 26 | 4 | 0.336 |
|  | *IDH1* |  | 12 | 11 | 1 | 1.000 |
|  | *IDH2* |  | 6 | 4 | 2 | 0.095 |
|  | *DNMT3A* |  | 4 | 4 | 0 | 1.000 |
|  | *TET2* |  | 8 | 7 | 1 | 0.537 |
| Tumor Suppressors | | | 54 | 44 | 10 | 0.018 |
|  | *WT1* |  | 40 | 31 | 9 | 0.005\* |
|  | *TP53* |  | 4 | 4 | 0 | 1.000 |
|  | *PHF6* |  | 14 | 13 | 1 | 1.000 |
| Cohesin | |  | 19 | 19 | 0 | 0.239 |
|  | *SMC1A* |  | 5 | 5 | 0 | 1.000 |
|  | *SMC3* |  | 6 | 6 | 0 | 1.000 |
|  | *RAD21* |  | 5 | 5 | 0 | 1.000 |
|  | *STAG2* |  | 1 | 1 | 0 | 1.000 |
|  | *NIPBL* |  | 2 | 2 | 0 | 1.000 |
| Spliceosome | |  | 11 | 9 | 2 | 0.263 |
|  | *SRSF2* |  | 2 | 1 | 1 | 0.174 |
|  | *U2AF1* |  | 6 | 5 | 1 | 0.438 |
|  | *SF3B1* |  | 1 | 1 | 0 | 1.000 |
|  | *ZRSR2* |  | 2 | 2 | 0 | 1.000 |
| *NPM1* | |  | 34 | 34 | 0 | 0.058 |

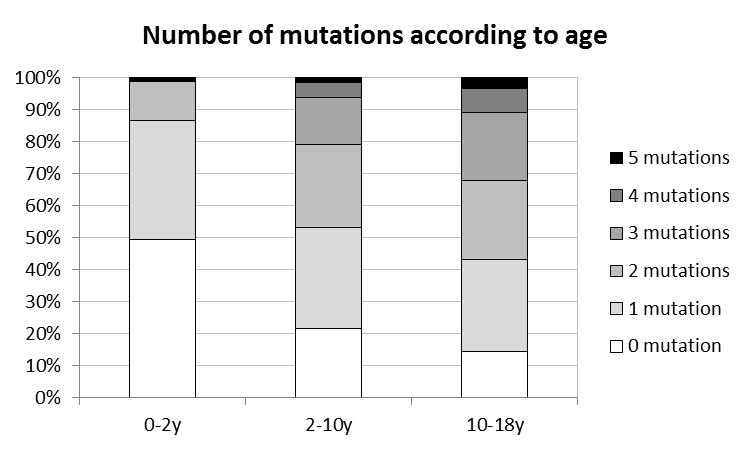
# Appendix Table S4: 3-years OS for molecular classifier subgroups.

|  |  |  |  |
| --- | --- | --- | --- |
| Molecular classifier subgroups | | Number of patients | 3-years OS |
| Favorable | | **142** | **92.1% [95%CI: 87.6-96.6]** |
|  | *NPM1* mutations | 34 | 97.1% |
|  | *CEBPA* double mutations | 16 | 87.1% |
|  | CBF translocations | 92 | 91.2% |
| Intermediate | | **184** | **73.2% [95%CI: 66.7-79.6]** |
|  | *KMT2A*-rearranged | 79 | 79.7% |
|  | Other profiles | 105 | 68.2% |
| Poor | | **59** | **46.1% [95%CI: 33.1-59.2]** |
|  | *NUP98* fusions | 10 | 25.0% |
|  | *PHF6* mutations | 9 | 44.4% |
|  | *RUNX1* mutations | 20 | 59.6% |
|  | *WT1* mutations | 20 | 42.8% |
| Total | | **385** | **76.1% [95%CI: 71.8-80.4]** |

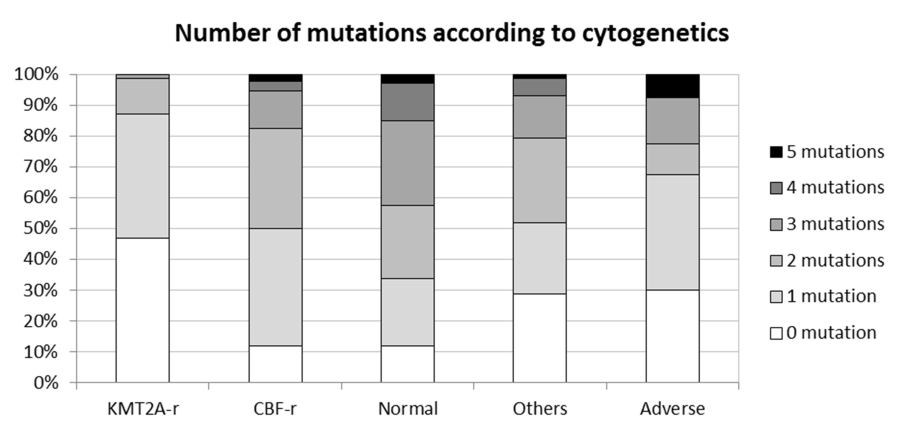
# Appendix Table S5: 3-years OS according to the 2017 ELN risk stratification.

|  |  |  |  |
| --- | --- | --- | --- |
| ELN classification | | Number of patients | 3-years OS |
|  | Favorable | 139 | 91.9% [95%CI: 87.4-96.5] |
|  | Intermediate | 139 | 67% [95%CI: 59.1-75] |
|  | Adverse | 107 | 67.2% [95%CI: 58.3-76.1] |

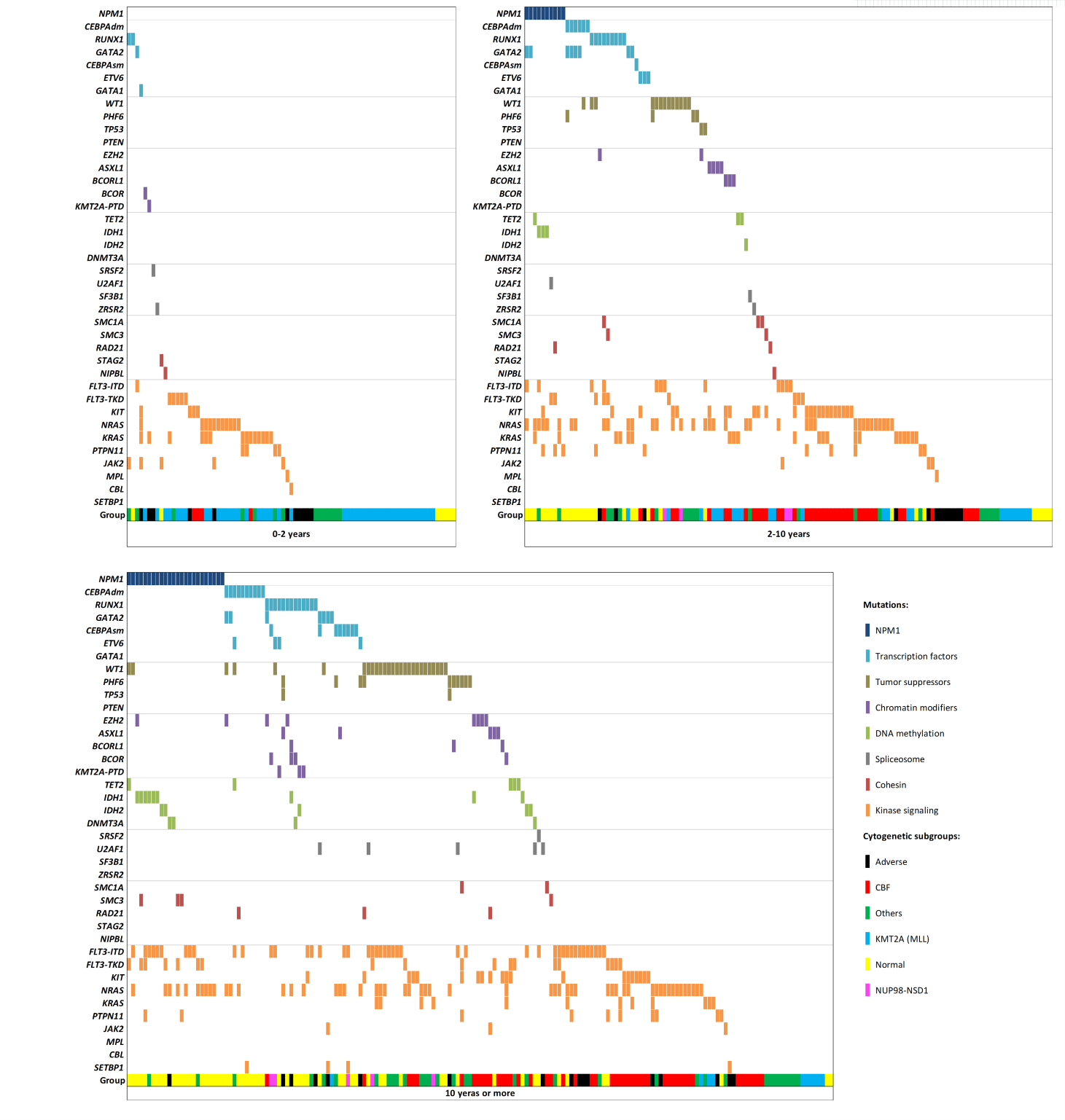
# Appendix Figure S1: Number of mutations according to age classes.



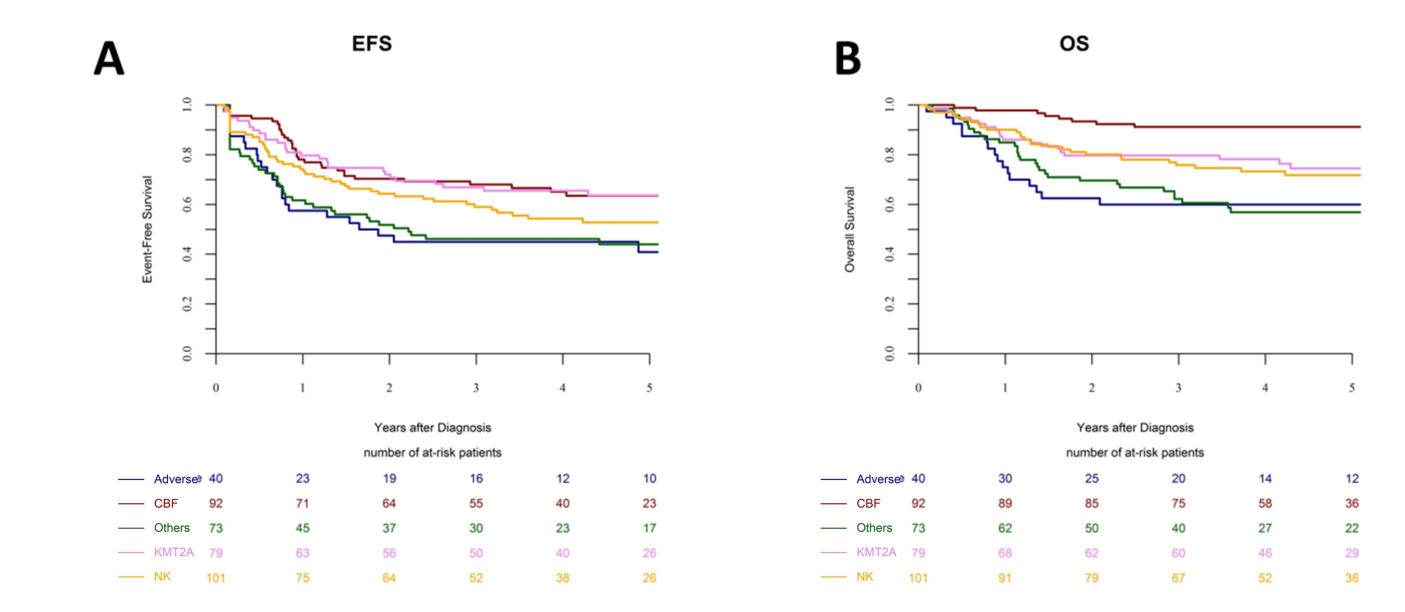
# Appendix Figure S2: Number of mutations according to cytogenetics.



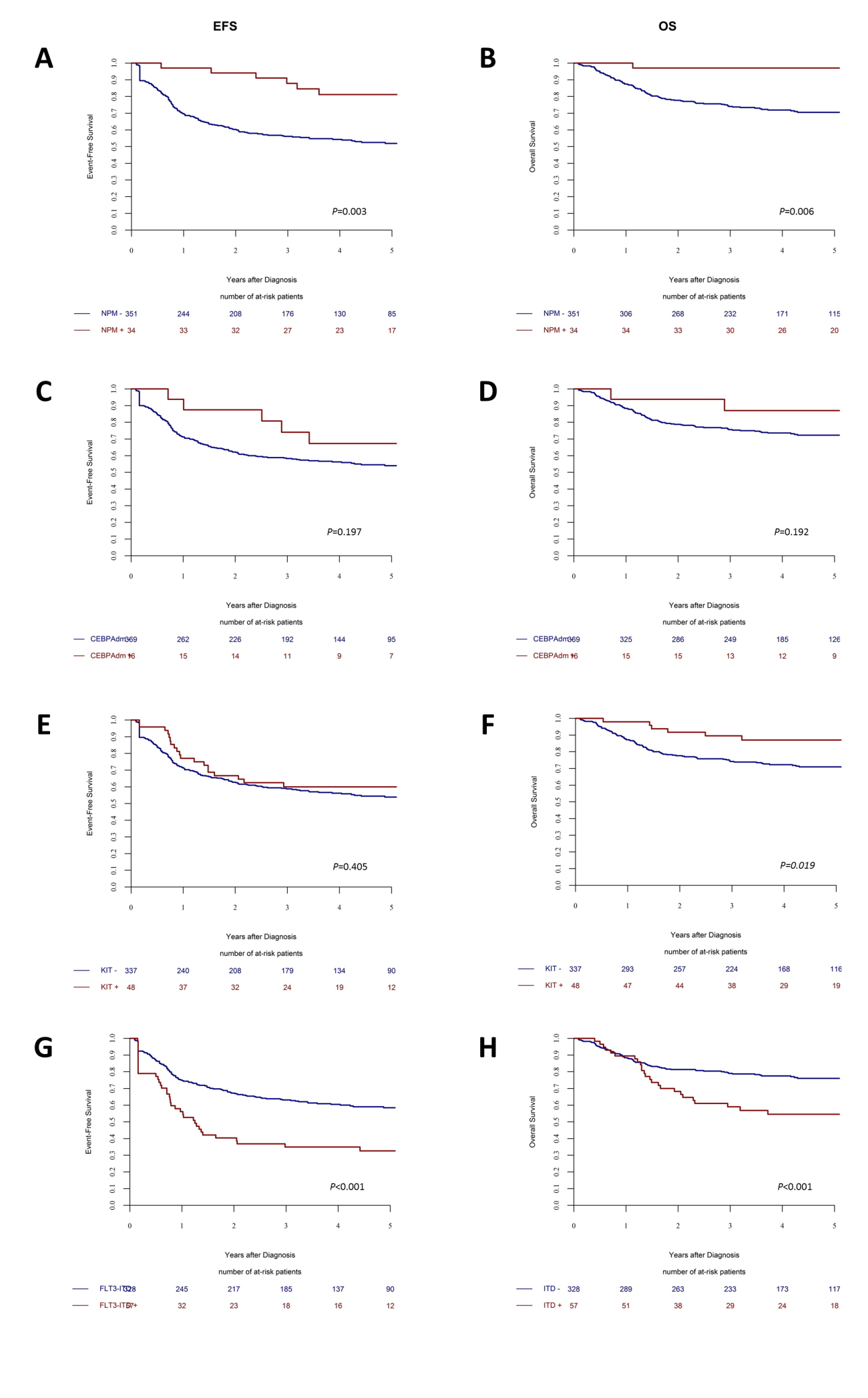
# Appendix Figure S3: Genomic landscape of childhood AML according to age groups (0-2 years; 2-10 years; 10 years or more). Each column represents the mutation pattern in one individual patient and each colored box represents a gene mutation.



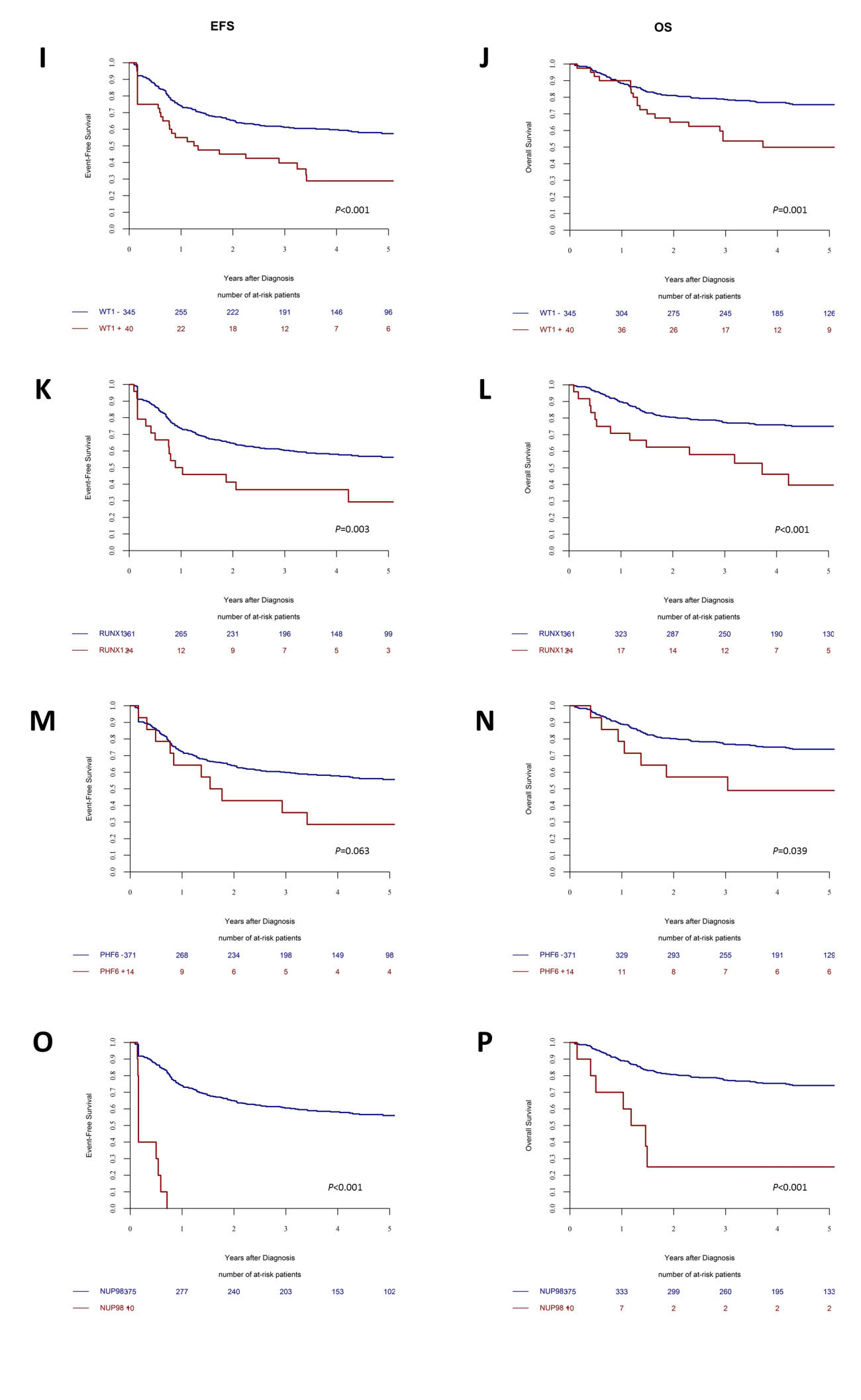
# Appendix Figure S4: Childhood AML outcome according to cytogenetic subgroups: normal karyotype (n=101, 26.2%), CBF-rearranged (n=92, 24%), *KMT2A*-rearranged (n=79, 21%), adverse karyotype (n=40, 10%) and other aberrations (n=73, 19%).



# Appendix Figure S5: Childhood AML outcome according to gene mutations. EFS and OS curves are shown for gene mutations which impact clinical outcome: *NPM1* (A-B), *CEBPAdm* (C-D), *KIT* (E-F), *FLT3-ITD* (G-H), *WT1* (I-J), *RUNX1* (K-L), *PHF6* (M-N) and *NUP98* fusions (O-P).



**(continued)**



# Appendix Figure S6: Impact of *FLT3-ITD* status in childhood AML with poor molecular risk (*NUP98*-rearrangements, *WT1*, *RUNX1* or *PHF6* mutations). Among patients with poor molecular risk (n=59), 22 were positive for *FLT3*-ITD.

