**Supplemental table 1** - On the left the 138 lymphoid-gene panel, on the right the 54 myeloid gene panel.

| LYMPHOID-GENE PANEL | MYELOID-GENE PANEL |
|----------------------|---------------------|
| AMOTL1               | ABL1                |
| APAF1                | FBXO11              |
| APC                  | MKI67               |
| ARID1A               | FBXW7               |
| ARID3A               | MSL2                |
| ATM                  | MYC                 |
| ATP6AP1              | ATRX                |
| ATP6V1B2             | KIT                 |
| B2M                  | FOXO1               |
| BCL10                | MYC                 |
| BCL2                 | NOTCH1              |
| BCL6                 | NOTCH2              |
| BCL7A                | NRAS                |
| BCL7B                | NPM1                |
| BCL7C                | NRAS                |
| BCOX1                | NOTCH1              |
| BIRC3                | P2RY8               |
| BRAF                 | PCDH10              |
| BTG1                 | PDE4DIP             |
| BTG2                 | POU2F2              |
| BTK                  | PTEN                |
| CARD11               | PTEN                |
| CCND1                | PTEN                |
| CCND2                | PTEN                |
| CCND3                | PTEN                |
| CCR6                 | PTEN                |
| CD58                 | PTEN                |
| CD70                 | PTEN                |
| CD79B                | PTEN                |
| CDKN2A               | PTEN                |
| CHD2                 | PTEN                |
| CIITA                | PTEN                |
| CREBBP               | PTEN                |
| CTNNB1               | PTEN                |
| CXCR4                | PTEN                |
| DDX3X                | PTEN                |
| DTX1                 | PTEN                |
| EBF1                 | PTEN                |
| EGR1                 | PTEN                |
| EGR2                 | PTEN                |
| EP300                | PTEN                |
| ETV6                 | PTEN                |
| EZH2                 | PTEN                |
| FAS                  | PTEN                |
| FAT1                 | PTEN                |
| FAT4                 | PTEN                |
| FAS                  | PTEN                |
| FAT1                 | PTEN                |
| FAT4                 | PTEN                |
Supplemental table 2 - Clinical features of the patients at diagnosis, chemotherapeutic regimens received, response and allogeneic bone marrow transplant

| Patient | Diagnosis (WHO 2016) | Age (y) | Induction CT | Response | Salvage CT | Response2 | ABMT |
|---------|----------------------|---------|--------------|----------|------------|-----------|------|
| Pt 2    | AUL                  | 66      | ALL-oriented | NR       | AML-oriented | CR        | yes  |
| Pt 3    | ALAL NOS             | 71      | ALL-oriented | CR       | -          | -         | no   |
| Pt 4    | ALAL NOS             | 46      | ALL-oriented | NR       | AML-oriented | NR       | yes  |
| Pt 5    | AUL                  | 72      | None         | -        | -          | -         | no   |
| Pt 6    | AUL                  | 72      | None         | -        | -          | -         | no   |
| Pt 7    | MPAL B/myeloid       | 52      | Lost to follow up | - | - | - | - |
| Pt 9    | MPAL B/myeloid bilinear | 63  | AML-oriented | CR       | -          | -         | yes  |
| Pt 10   | MPAL T/myeloid       | 45      | AML-oriented | CR       | -          | -         | yes  |
| Pt 11   | AUL                  | 73      | ALL-oriented | CR       | -          | -         | NA   |
| Pt 12   | AUL                  | 26      | ALL-oriented | CR       | -          | -         | NA   |
## Supplemental Table 3 - Oncogenic and likely oncogenic SNV and small indels per patient

| Pt | Gene      | Function          | Chr | Exon | WT | MT          | VAF  | C.               | P.     | Tag        |
|----|-----------|-------------------|-----|------|----|-------------|------|-------------------|--------|------------|
| 2  | ASXL1     | frameshift deletion | 20  | 12   | -  | G           | 0.50 | c.1927dupG       | p.G642fs | oncogenic  |
| 2  | BOCR      | stopgain SNV      | X   | 14   | C  | A           | 0.07 | c.G4810T         | p.E1604X | oncogenic  |
| 2  | EZH2      | frameshift deletion | 7   | 10   | T  | -           | 0.91 | c.1211delA       | p.E404fs | oncogenic  |
| 2  | RUNX1     | missense          | 21  | 5    | A  | T           | 0.43 | c.T488A          | p.F163Y  | oncogenic  |
| 2  | RUNX1     | stopgain SNV      | 21  | 7    | -  | A           | 0.42 | c.777dupT        | p.N260STOP261delinsX | oncogenic  |
| 2  | KMT2C     | missense          | 7   | 14   | G  | A           | 0.0452 | c.C2291T       | p.S764F  | oncogenic  |
| 2  | KMT2D     | frameshift deletion | 12  | 31   | A  | -           | 0.3125 | c.6595delT      | p.Y2199fs | oncogenic  |
| 3  | DNMT3A    | missense          | 2   | 19   | T  | A           | 0.06 | c.A2321T         | p.E774V  | oncogenic  |
| 3  | DNMT3A    | missense          | 2   | 23   | G  | A           | 0.37 | c.C2644T         | p.R882C  | oncogenic  |
| 3  | IDH2      | missense          | 15  | 4    | C  | T           | 0.19 | c.G419A          | p.R140Q  | oncogenic  |
| 3  | NRAS      | missense          | 1   | 2    | C  | T           | 0.18 | c.G34A           | p.G12S   | oncogenic  |
| 3  | NOTCH1    | missense          | 9   | 27   | A  | T           | 0.1042 | c.T5033A       | p.L1678Q | oncogenic  |
| 4  | BOCR      | missense          | X   | 8    | G  | T           | 0.04 | c.C3719A         | p.S1240Y | oncogenic  |
| 4  | ARID1A    | missense          | 1   | 9    | A  | G           | 0.1644 | c.A2825G       | p.N942S  | oncogenic  |
| 4  | KMT2C     | stopgain SNV      | 7   | 7    | A  | C           | 0.0263 | c.T918G        | p.Y306X  | oncogenic  |
| 5  | ASXL1     | frameshift deletion | 20  | 12   | GT | -           | 0.3  | c.2058_2059del   | p.686_687del | oncogenic  |
| 6  | ASXL1     | stopgain SNV      | 20  | 11   | C  | T           | 0.43 | c.C1210T         | p.R404X  | oncogenic  |
| 6  | FLT3      | missense          | 13  | 20   | T  | A           | 0.08 | c.A2504T         | p.D835V  | oncogenic  |
| 6  | KRAS      | missense          | 12  | 2    | T  | A           | 0.14 | c.A15T           | p.K5N    | oncogenic  |
| 6  | NRAS      | missense          | 1   | 2    | C  | A           | 0.04 | c.G37T           | p.G13C   | oncogenic  |
| 6  | SETBP1    | missense          | 18  | 4    | G  | A           | 0.42 | c.G2602A         | p.D868N  | oncogenic  |
| 6  | SRFSF2    | missense          | 17  | 1    | G  | T           | 0.40 | c.C284A          | p.P95H   | oncogenic  |
| 7  | IKZF1     | missense          | 7   | 5    | C  | T           | 0.25 | c.C484T          | p.R162W  | oncogenic  |
| 7  | KDM6A     | frameshift deletion | X  | 23   | TA | TC A        | -0.54 | c.3338_3342del   | p.1113_1114del | oncogenic  |
| 7  | NRAS      | missense          | 1   | 2    | C  | T           | 0.46 | c.G34A           | p.G12S   | oncogenic  |
| 7  | PDE4DIP   | missense          | 1   | 1    | G  | T           | 0.1608 | c.C100A        | p.C34K   | oncogenic  |
| 9  | PHF6      | missense          | X   | 9    | C  | G           | 0.80 | c.C932G          | p.A311G  | oncogenic  |
| 9  | RUNX1     | missense          | 21  | 4    | T  | C           | 0.37 | c.A314G          | p.H105R  | oncogenic  |
| 9  | RUNX1     | frameshift deletion | 21  | 5    | G  | -           | 0.26 | c.492delC        | p.V164fs | oncogenic  |
| 9  | SF3B1     | missense          | 2   | 13   | C  | T           | 0.43 | c.G1774A         | p.E592K  | oncogenic  |
| 9  | FGFR3     | missense          | 4   | 7    | C  | T           | 0.53 | c.C899T          | p.P300L  | oncogenic  |
| 10 | PHF6      | missense          | X   | 10   | A  | G           | 0.34 | c.A974G          | p.Y325C  | oncogenic  |
| 10 | ATM       | stopgain SNV      | 11  | 51   | A  | T           | 0.875 | c.A7516T        | p.R2506X | oncogenic  |
| 11 | DNMT3A    | missense          | 2   | 19   | G  | A           | 0.07 | c.C2245T         | p.R749C  | oncogenic  |
| 11 | NRAS      | missense          | 1   | 2    | C  | T           | 0.05 | c.G35A           | p.G12D   | oncogenic  |
| 11 | RUNX1     | nonsense          | 21  | 5    | C  | A           | 0.04 | c.G427T          | p.E143*  | oncogenic  |
| 11 | RUNX1     | inframe insertion | 21  | 5    | -  | TAGC ATCT AC | 0.05 | c.442_443insGAGATGCTA | p.A147_T148insrDA | likely oncogenic  |
| 11 | U2AF1     | missense          | 21  | 2    | G  | A           | 0.07 | c.C101T          | p.S34F   | oncogenic  |
| Gene   | Mutation Type | Chromosome | Start Position | End Position | Nucleotide Change | Amino Acid Change | Status   |
|--------|---------------|------------|----------------|--------------|-------------------|--------------------|----------|
| EZH2   | missense      | 12         | 17             | G            | A                 | 0.2                | p.S652F  |
| PTPN11 | missense      | 12         | 3              | G            | A                 | 0.47               | p.D61N   |
| RUNX1  | frameshift insertion | 21  | 5              | CTCT         | c.382_383insA     | p.T128Kfs*11      | oncogenic|
| RUNX1  | missense      | 21         | 5              | G            | C                 | 0.43               | p.R166G  |
| U2AF1  | missense      | 21         | 6              | C            | T                 | 0.2                | p.R156H  |
**Supplemental figure 1** - Median number of mutations in myeloid genes (3, IQR: 1-4) compared to the lymphoid ones (1, IQR: 0-1) (Wilcoxon matched-pairs signed-rank test p=0.012)
Supplemental Figure 2 - RUNX1 c.488T>A variant oncogenic mechanism in patient 2.
The nucleotide mutation is highlighted in green. RUNX1 exon 5 (NM_001754) is highlighted in yellow, introns are not highlighted. The sequence in the box represents the canonical splice site where, in normal conditions, the splicing machinery cuts the DNA. The sequence underscored within exon 5 represents the cryptic splice site region. The splicing predictive score of the canonical splice site is high (Fruitfly 0.99), compared with the wild type sequence of the cryptic splice site region (Fruitfly 0.47). However, the presence of the c.488T>A variant markedly increases the prediction score of the cryptic splice site sequence (Fruitfly 1.00). According to this prediction, RNA reads obtained from patient 2 show the presence of a 23-nucleotide deletion (c.486-508del23). Therefore, we hypothesize that the oncogenic mechanism resides in the erroneous recognition of the cryptic splice site sequence by the splicing machinery, thus resulting in the cut of the last 23 nucleotides of exon 5. This non-canonical splice site recognition ultimately induces a shift in the reading frame predicted to cause a truncated RUNX1 protein (p.F163EfsX41).

ATCATTGAATATACATTTTAATTTTAGAATAATCACTACACAAATGCCCTAAAAGTGTATG
TATAACATCCCTGATGTCAGTTCTTTGACTGGTGGGTTTAGGTGGTGCCCTAG
GGATGTTCAGAGCGACTCTGCTACGTGATGGAATGGGATCTGGAAATGCTACCGCA
GCCATGAAACCAGTGCAGTCAGT
AGTGCAAGACTCTACGCTTATG
AGGCAACAGCTTCTGCTACCTGGCAGAAGGAGTACGTTAAGCTGTCAGTTATGC
AAGCAATCAGTTCTGCTACCTGCTTACCTTG
TCCCTAGAAGACTCGGTCTCCTTACATTTGCTATGCTACGCTTTA
Supplemental Figure 3 - Circos plot representing gene pathways and mutations in ALAL subtypes