**Supplementary Table S1. Univariate analysis on the whole cohort of 132 LBL patients.**

| Characteristics | Categories | N° patients | Events | 4-year PFS % (SE%) | Univariate p-value |
|---|---|---|---|---|---|
| Treatment protocol | LNH97 | 29 | 6 | 82 (7) | 0.72 |
| | EuroLB02 | 103 | 15 | 84 (4) | |
| Age | <8.3 years | 66 | 11 | 83 (5) | 0.86 |
| | ≥8.3 years | 66 | 10 | 83 (5) | |
| Gender | Male | 92 | 16 | 81 (4) | 0.46 |
| | Female | 40 | 5 | 87 (5) | |
| Stage | I+II | 9 | 0 | 100 - | 0.18 |
| | III+IV | 123 | 21 | 79 (4) | |
| Immunophenotype | T | 107 | 17 | 83 (4) | 0.87 |
| | pB | 25 | 4 | 82 (8) | |
| BM involvement | Yes | 43 | 2 | 92 (4) | 0.0686 |
| | No | 89 | 19 | 79 (5) | |
| Mediastinal involvement | Yes | 89 | 15 | 82 (4) | 0.61 |
| | No | 43 | 6 | 85 (6) | |
| CNS involvement | Yes | 12 | 2 | 83 (11) | 0.77 |
| | No | 120 | 19 | 83 (4) | |
| MDD | <3% cut-off | 93 | 15 | 82 (4) | 0.82 |
| | ≥3% cut-off | 39 | 6 | 85 (6) | |
| Mutational status* | N/Fmut | 24 | 0 | 100 | 0.0032 |
| | N/Fwt | 34 | 10 | 64 | |

T: T-cell; pB: B-cell precursor; MDD: minimal disseminated disease; N/Fmut: *NOTCH/FBXW7* mutated; N/Fwt: *NOTCH/FBXW7* wild-type.
*data were available only for 58 T-LBL patients.

**Supplementary Table S2. Univariate analysis on the 83 LBL patients in stage I-III.**

| Characteristics | Categories | N° patients | Events | 4-year PFS % (SE%) | Univariate p-value |
|---|---|---|---|---|---|
| Treatment protocol | LNH97 | 19 | 5 | 78 (10) | 0.84 |
| | EuroLB02 | 64 | 13 | 77 (5) | |
| Age | < 8.3 years | 43 | 9 | 79 (7) | 0.87 |
| | ≥ 8.3 years | 40 | 9 | 79 (7) | |
| Gender | Male | 61 | 13 | 78 (6) | 0.46 |
| | Female | 22 | 5 | 77 (9) | |
| Immunophenotype | T | 65 | 14 | 78 (5) | 0.94 |
| | pB | 18 | 4 | 74 (12) | |
| MDD | <3% cutoff | 76 | 14 | 80 (5) | 0.068 |
| | ≥3% cutoff | 7 | 4 | 57 (19) | |
| Mediastinal involvement | Yes | 58 | 13 | 76 (6) | 0.69 |
| | No | 25 | 5 | 80 (9) | |
| Mutational status* | N/Fmut | 18 | 0 | 100 | 0.0013 |
| | N/Fwt | 21 | 9 | 64 | |

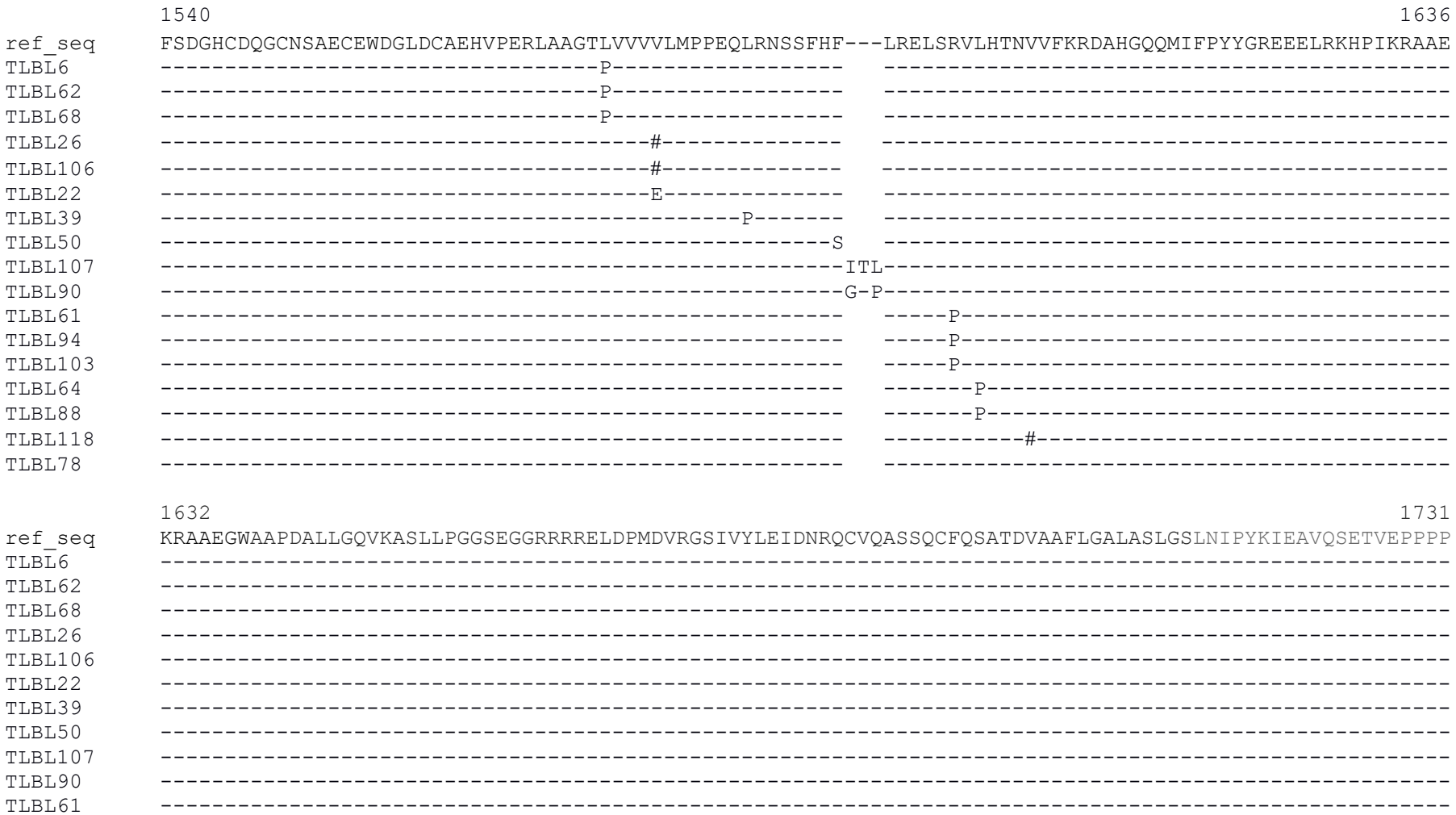
T: T-cell; pB: B-cell precursor; MDD: minimal disseminated disease; N/Fmut: *NOTCH/FBXW7* mutated; N/Fwt: *NOTCH/FBXW7* wild-type.
*data were available only for 39 T-LBL patients.

**Supplementary Table S3**: List of NOTCH1/FBXW7 mutations identified in 24 T-LBL patients. Sequence numbering is based on GenBank accessions NM_017617.4/NP_060087.3 for NOTCH1 and NM_033632.3/NP_361014.1 for FBXW7.

| | ***NOTCH1*** **HD domain** | | ***NOTCH1*** **PEST domain** | | ***FBXW7*** | |
|---|---|---|---|---|---|---|
| **patient** | **DNA** | **protein** | **DNA** | **protein** | **DNA** | **protein** |
| TLBL6 | c.4721T>C | p.L1574P | | | c.1393C>T<br>c.2065C>T | p.R465C<br>p.R689W |
| TLBL21 | | | c.7541-42delCT | p.S2513fs*3 | | |
| TLBL22 | c.4733T>A | p.V1578E | c.7354-55insGA | p.L2451fs*25 | | |
| TLBL26 | c.4732-34del | p.V1578del | c.7538-39del | p.P2514* | | |
| TLBL30 | | | c.7397C>T | p.T2466M | | |
| TLBL36 | | | | | | |
| TLBL39 | c.4754T>C | p.L1585P | | | | |
| TLBL50 | c.4775T>C | p.F1592S | | | | |
| TLBL58 | | | | | c.1552G>A | p.A518T |
| TLBL61 | c.4793G>C | p.R1598P | | | | |
| TLBL62 | c.4721T>C | p.L1574P | | | | |
| TLBL64 | c.4799T>C | p.L1600P | | | | |
| TLBL68 | c.4721T>C | p.L1574P | c.7130-37del>insTCGCGAA | p.P2410fs*10 | | |
| TLBL72 | | | c.7389-401del>insTCC | p.A2463fs*9 | c.1394G>A | p.R465H |
| TLBL78 | c.5101G>C<br>c.5153T>C | p.A1701P<br>p.I1718T | c.7541-42del | p.S2513fs*3 | | |
| TLBL88 | c.4799T>C | p.L1600P | | | | |
| TLBL90 | c.4775-76insTGGCCC | p.F1592insGP | | | c.1429G>A | p.G477S |
| TLBL94 | c.4793G>C | p.R1598P | | | | |
| TLBL103 | c.4793G>C | p.R1598P | | | | |
| TLBL106 | c.4732-34del | p.V1578del | | | | |
| TLBL107 | c.4775-76insGATACC | p.F1592>LIT | | | | |
| TLBL118 | c.4810-12del | p.V1604del | c.7533-7541del | p.P2512* | | |
| TLBL119 | | | c.7327G>AGCCCC | p.D2442fs*35 | | |
| TLBL125 | | | c.7400 C>A | p.S2467* | | |

**Supplementary Figure S1**: Multiple sequence alignment of NOTCH1 wild-type and variants identified in the present study. Number of first and last depicted amino acids of reference sequence (ref_seq) are indicated based on NP_060087.3. Sequence differences caused by missense mutations, insertions or frame-shifts are shown.
* stop codon
# deleted codon

**NOTCH1 HD domain**



```
TLBL94      ----------------------------------------------------------------------------------------------------
TLBL103     ----------------------------------------------------------------------------------------------------
TLBL64      ----------------------------------------------------------------------------------------------------
TLBL88      ----------------------------------------------------------------------------------------------------
TLBL118     ----------------------------------------------------------------------------------------------------
TLBL78      ----------------------------------------------------------P----------------T-------------
```

**NOTCH1 PEST DOMAIN**

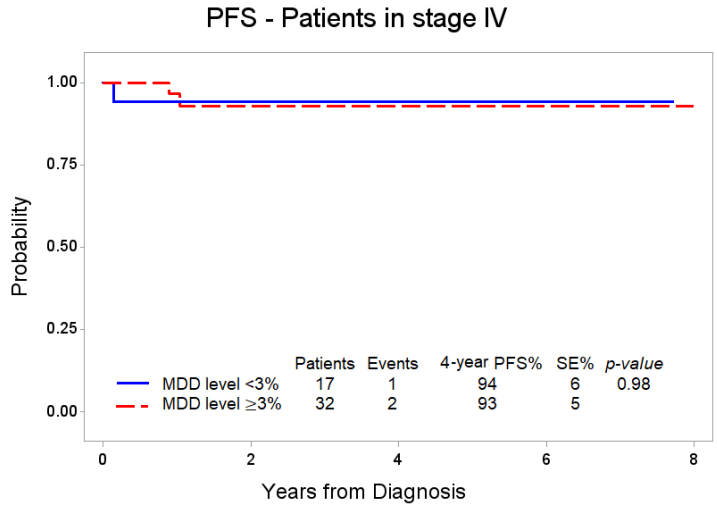
```
            2379                                                                                          2478
ref_seq     LVQTQQVQPQNLQMQQQNLQPANIQQQQSLQPPPPPPQPHLGVSSAASGHLGRSFLSGEPSQADVQPLGPSSLAVHTILPQESPALPTSLPSSLVPPVTA
TLBL30      ----------------------------------------------------------------------------------------M------------
TLBL21      ----------------------------------------------------------------------------------------------------
TLBL78      ----------------------------------------------------------------------------------------------------
TLBL26      ----------------------------------------------------------------------------------------------------
TLBL118     ----------------------------------------------------------------------------------------------------
TLBL119     ------------------------------------------------------------SPCSHWAPAAWWCTLFCPRRAPPCPRRCHPRWSHP*
TLBL22      ----------------------------------------------------------------------GRCTLFCPRRAPPCPRRCHPRWSHP*
TLBL72      ----------------------------------------------------------------------------------PCHPRWSHP*
TLBL125     ----------------------------------------------------------------------------------------*
TLBL68      --------------------------------REHHHSRTLA*
```

```
            2479                                                                  2556
ref_seq     AQFLTPPSQHSYSSPVDNTPSHQLQVPEHPFLTPSPESPDQWSSSSPHSNVSDWSEGVSSPPTSMQSQIARIPEAFK*
TLBL30      ------------------------------------------------------------------------
TLBL21      ----------------------------------RVP*
TLBL78      ----------------------------------RVP*
TLBL26      ----------------------------------*
TLBL118     ----------------------------------*
LBL119
TLBL22
TLBL72
TLBL125
TLBL68
```

**Supplementary Figure S2**: Multiple sequence alignment of FWBX7 wild-type and variants identified in the present study. Number of first and last depicted amino acids of reference sequence (ref_seq) are indicated based on NP_361014.1. Sequence differences caused by missense mutations are shown.
* stop codon

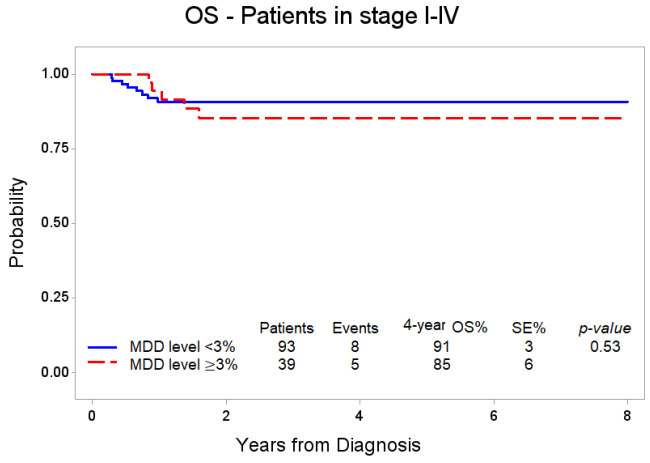
```
            422                                                                                                 521
ref_seq     GGVWSSQMRDNIIISGSTDRTLKVWNAETGECIHTLYGHTSTVRCMHLHEKRVVSGSRDATLRVWDIETGQCLHVLMGHVAAVRCVQYDGRRVVSGAYDF
TLBL6       ------------------------------------------C-------------------------------------------------------
TLBL72      ------------------------------------------H-------------------------------------------------------
TLBL90      ----------------------------------------------------S-----------------------------------------------
TLBL58      ------------------------------------------------------------------------------------------------T---


            618                                                                   708
ref_seq     QGPNKHQSAVTCLQFNKNFVITSSDDGTVKLWDLKTGEFIRNLVTLESGGSGGVVWRIRASNTKLVCAVGSRNGTEETKLLVLDFDVDMK*
TLBL6       ------------------------------------------------------------------W-------------------
TLBL72      ----------------------------------------------------------------------------------------
TLBL90      ----------------------------------------------------------------------------------------
TLBL58      ----------------------------------------------------------------------------------------
```

**Supplementary Figure S3**. 4-year PFS of stage IV LBL patients (N=49) stratified according to MDD levels above or below the 3% cut-off

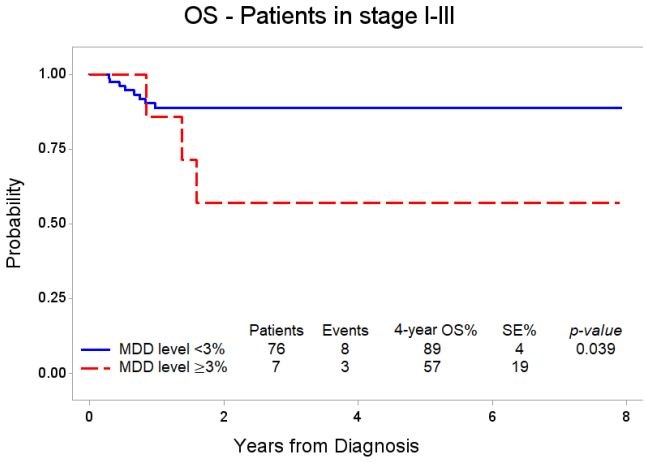



The same analysis on stage IV patients without CNS involvement (N=37) showed a 4-year PFS of 100% and 96% (± 4%) for patients with MDD <3% and ≥3% (p-value 0.56), respectively.
As for stage IV patients with CNS involvement (N=12), 4-year PFS was 88% (± 13%) for patients with MDD <3% (8/12), whereas patients with MDD≥3% (4/12) had a 4-year PFS of 75% (± 25%). No statistically significant difference was observed (p-value 0.69).

**Supplementary Figure S4**. 4-year OS according to MDD levels above or below the 3% cut-off: (a) all LBL patients with available MDD results; (b) LBL patients in stage I-III.

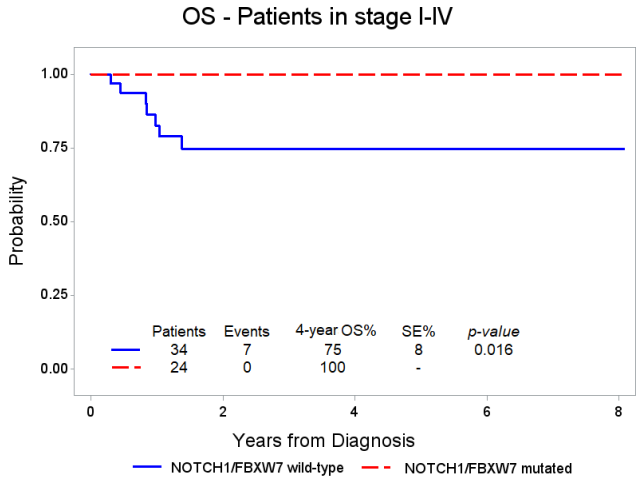



(a)

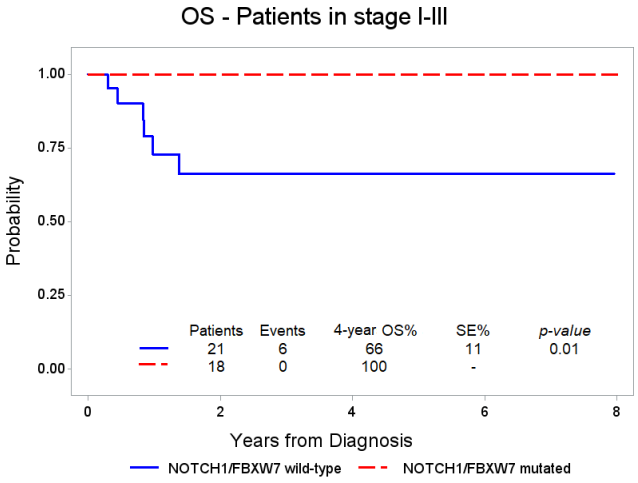



(b)

**Supplementary Figure S5.** 4-year OS according to *NOTCH1/FBXW7* mutational status: (a) all T-LBL patients with available N/F mutations data; (b) T-LBL patients in stage I-III.




(a)




(b)

**Supplementary Figure S6.** 4-year OS according to MDD levels and *NOTCH1/FBXW7* mutational status in uniformly treated T-LBL patients without morphological BM involvement (stages I-III).