# Supplemental Material

**Statistical analysis**

The aim of this study was an exploratory analysis and a statistical evaluation of the differences between mutated (M-CLL) versus unmutated (U-CLL) patients regarding risk evolution for CLL progression and need of treatment. To assess the risk for disease progression, we evaluated the time-to-first-treatment (TTFT) from the date of initial diagnosis within different subgroups of Binet A patients. These subgroups were defined based on particular genomic aberrations. In the entire cohort as well as in each genomic subgroup, the risk regarding the need for treatment was evaluated separately for M-CLL and U-CLL, with risk evolution over-time being presented by a hazard curve.

The Kaplan–Meier survival curves are the gold standard approach for visually assessing the impact of a specific biomarker on survival. An alternative suggestion can be the use of hazard curves. The main advantage of the hazard curve compared to the Kaplan-Meier survival curve is that it represents the "instant" risk for the event at each time-point, instead of the cumulative risk.

Smoothed estimates of the hazard curve were computed, based on a non-parametric methodology resulting in smoothed hazard plots ("bshazard" package, R). A hazard curve shows the estimated proportion of patients who received treatment for the first time in a defined time interval, given that they were still treatment-free at the start of this interval. On the other hand, a Kaplan-Meier survival curve estimates the proportion of patients who are treatment-free at a specific time-point. The hazard plots are displayed along with the usual Kaplan-Meier survival plots to strengthen the understanding of risk evolution but also for comparison reasons.

To evaluate and compare the evolution pattern of the M-CLL and U-CLL hazard curves for each subgroup, we investigated over-time both their hazard differences, and their hazard ratios. An interpolation method was initially used to estimate the values of the hazard curve at each distinct year from the time of diagnosis. The hazard differences between M-CLL and U-CLL were computed at each distinct year from the

time of diagnosis. Years 5, 10 and 15 after diagnosis were considered as landmark time-points for over-time comparison. Then, the distributions of hazard differences were statistically compared between consecutive 5-year intervals with a non-parametric test (Mann-Whitney) to assess the evolution over-time (trend) of the distance between the hazard curves of the M-CLL and U-CLL patients. P-values less than 0.05 might indicate convergence or divergence of the curves within consecutive 5-year intervals. When more than 10 years of follow-up were assessed, an overall p-value was also calculated (Kruskal-Wallis test), which signified the overall comparison of hazard differences' distributions for the whole time span considered in each case (overall p-values are given in Supplemental Table 2). In all other cases the overall p-value was identical to the p-value. All tests were two-sided. For both the entire cohort as well as del(13q)/normal FISH patients, the time span reached up to 20 years, while for the remaining subgroups, the corresponding time span was limited to the first 10 years due to their more aggressive clinical courses and the limited number of available events after the $10^{th}$ year.

Regarding the hazard ratios for M-CLL and U-CLL, they were also computed at each distinct year from the time of diagnosis. In addition, the proportional hazards assumption was checked, based on the Schoefeld residuals, as it would be typically checked when applying a simple Cox model with SHM status being the sole predictor (see Supplemental Table 2 and Supplemental Figure 9). The proportional hazards assumption meaning in this case is that the hazard ratio between a U-CLL and a M-CLL patient does not depend on time. Significant differences and/or variation in the hazard ratio over-time could cause the rejection of the assumption, and solidify even further the need for an over-time analysis of the hazard evolution.

Finally, we have applied a methodological approach, which describes the survival using a piecewise exponential distribution with possible changepoints that indicate statistically significant changes of hazard rates. Identifying such break points might further contribute in understanding hazard rate evolution. This analysis was based on the "RPEXE.RPEXT" package in R. Although our results did not detect any significant changepoints in terms of the hazard rates, the backward elimination procedure of the method tended to

eliminate at the final spots, time-points very close to the 5th year or similar and in accordance with the remaining results. Thus, we feel that this method supports our results (and more data within specific subgroups could potentially enable successfully detecting changepoints). Particularly, the results regarding *TP53*abn cases are displayed in the Supplemental Table 3.

The analysis was performed with R.

**Supplemental Table 1:** Main clinicobiological features of the entire cohort.

| | Entire cohort<br>n, % | M-CLL<br>n, % | U-CLL<br>n, % |
|---|---|---|---|
| **Gender** | | | |
| Male | 1117/1900, 59% | 711/1224, 58% | 406/676, 60% |
| **Age at Diagnosis** | | | |
| Median age (years) | 63·8 (22-92) | 63·4 (22-91) | 64·5 (34-92) |
| **CD38 expression** | | | |
| High | 205/1399, 15% | 127/1186, 11% | 78/213, 37% |
| **FISH detected abnormalities** | | | |
| idel(13q) | 584/1172, 50% | 459/906, 51% | 125/266, 47% |
| Trisomy 12 | 204/1456, 14% | 96/933, 10% | 108/523, 21% |
| del(11q) | 141/1468, 10% | 23/939, 2·4% | 118/529, 22% |
| del(17p) | 69/1476, 4·7% | 30/948, 3·2% | 39/528,7·4% |
| **Recurrent gene mutations** | | | |
| *MYD88* | 16/709, 2·3% | 16/436, 3·7% | 0/273, 0% |
| *NOTCH1* | 103/1691, 6·1% | 15/1104, 1·4% | 88/587, 15% |
| *SF3B1* | 65/1166, 5·6% | 20/750, 2·7% | 45/416, 11% |
| *TP53* | 89/1186, 8% | 35/656, 5·3% | 54/530, 10% |
| *BIRC3* | 14/634, 2·2% | 5/393, 1·3% | 9/241, 3·7% |
| ***TP53*abn** | 119/1671, 7·1% | 46/1035, 4·4% | 73/636, 11% |
| **Immunogenetic features** | | | |
| GI: 97-97·99% | 80/1900, 4·2% | 80/1224, 6·5% | - |
| GI: 100% | 502/1900, 26% | - | 502/676, 74% |
| Stereotyped #1 | 34/1779, 1·9% | - | 34/555, 6·1% |
| Stereotyped #2 | 17/1779, 1% | 13/1224, 1·1% | 4/555, 0·7% |
| Stereotyped #4 | 32/1900, 1·7% | 32/1224, 2·6% | - |
| **Additional Information** | | | |
| **Median (95% CI)**<br>Time to first treatment | 10·5 (9·4-12·9) | 28·4 (20·20-NA) | 3·31 (2·93-3·78) |
| **Number of events** | 738/1900, 38·8% | 286/1224, 23·4% | 452/676, 66·9% |

U-CLL: CLL with unmutated IGHV genes; M-CLL: CLL with mutated IGHV genes; idel(13q): isolated del(13q); GI: germline identity; CI: confidence interval; high CD38: CD38 positive cells >30%; stereotyped #1, #2, #4: stereotyped subset #1, #2, #4.

**Supplemental Table 2:** The p-values of the overall comparison within consecutive 5-year intervals of the distributions of hazard differences between M-CLL and U-CLL are displayed in the first row for all the subgroups considered. The p-values referring to the evaluation of the proportional hazards assumption, based on the Schoefeld residuals are displayed in the second row for all the subgroups considered. The assumption of proportional hazards between M-CLL and U-CLL was rejected only for patients with *TP53* aberrations [*TP53*abn, del(17p) and/or *TP53* mutations] with p-value=0.045. This signified statistically significant differences in the hazard ratio between U-CLL and M-CLL *TP53*abn patients over-time, reflecting the great variation observed for the hazard ratios in the case of *TP53*abn patients, ranging from 1.75 (at diagnosis) to 8.09 ($10^{th}$ year). In all other cases, the deviation from over-time hazard proportionality was not statistically different.

| | | Binet A | *TP53*abn | del(11q) (no *TP53*abn ) | +12 (no *TP53*abn ) | del(13q)/ normal FISH | *NOTCH1* | *SF3B1* |
|---|---|---|---|---|---|---|---|---|
| Over-time differences | overall p-value | **<0.001** | **0.006** | **0.006** | **0.006** | **<0.001** | **0.006** | 0.465 |
| Proportional hazard assumption | p-value | 0.381 | **0.045** | 0.550 | 0.365 | 0.787 | 0.603 | 0.243 |

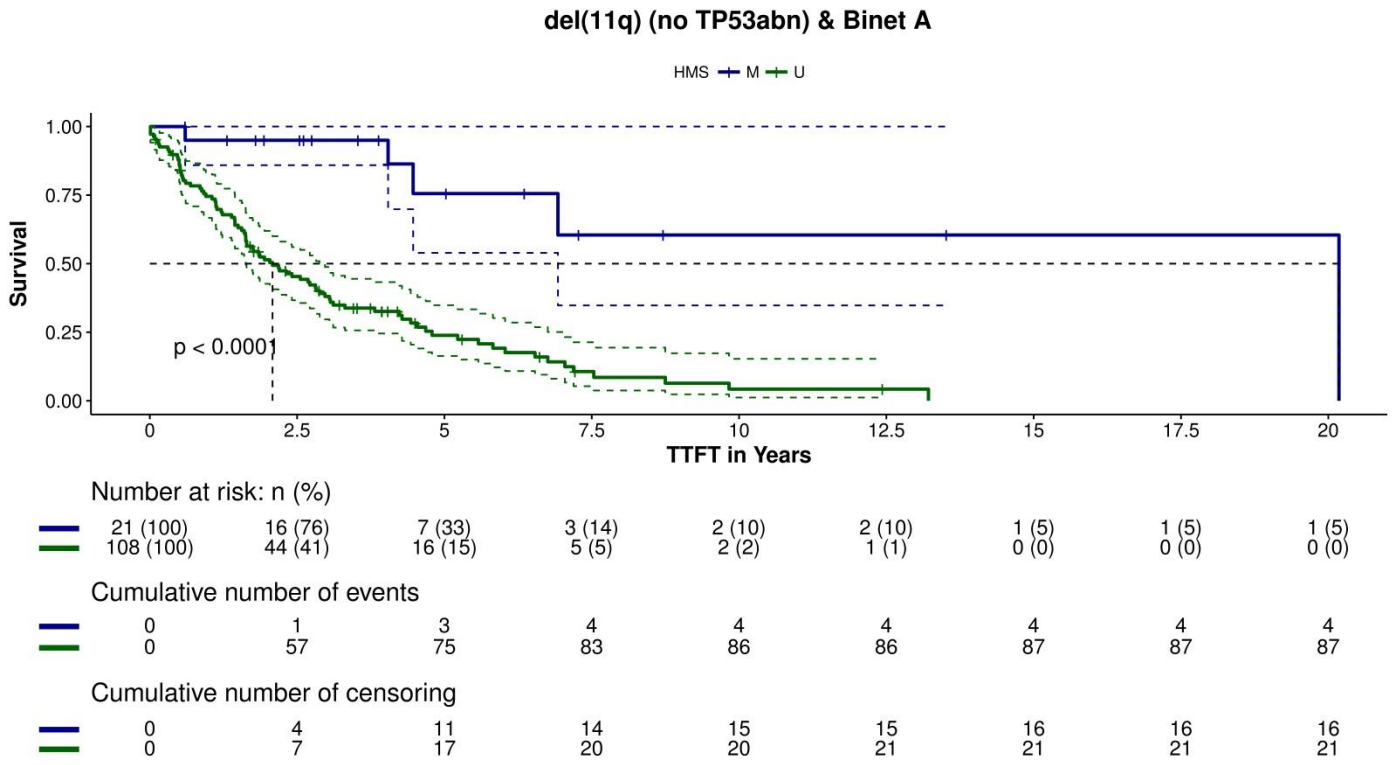
**Supplemental Table 3:** The results of a piecewise exponential methodological approach, which describes the survival using a piecewise exponential distribution with possible changepoints that indicate statistically significant changes of hazard rates, are displayed for cases with *TP53* aberrations [*TP53*abn, del(17p) and/or *TP53* mutations], separately for the M-CLL and the U-CLL. The first column indicates the candidate changepoints assessed, the second column the respective p-value (less than critical value a* would indicate that the specific time-point is a changepoint), and the third column represents the result of the evaluation of each time-point ("Eliminated" signifies that the point has not been recognized as a changepoint). The proposed time-points are the ones which were the nearest with observed events to the time-points 1.25, 2.5, 3.75, 5, 6.25, etc., which are the time-points that divide the interval (0,10) to 8 equal-distanced time intervals. In both cases, the results refer to the application of the method without order restriction. The order of the time-points in the tables below represents the order of elimination. The analysis was based on the "RPEXE.RPEXT" package.

| M-CLL | | |
|---|---|---|
| **Time-points** | **P-value** | **Action** |
| 8.27 | 0.96 | Eliminated |
| 1.25 | 0.91 | Eliminated |
| 5.34 | 0.84 | Eliminated |
| 3.85 | 0.90 | Eliminated |
| 10.93 | 0.84 | Eliminated |
| 2.39 | 0.02 | Eliminated |

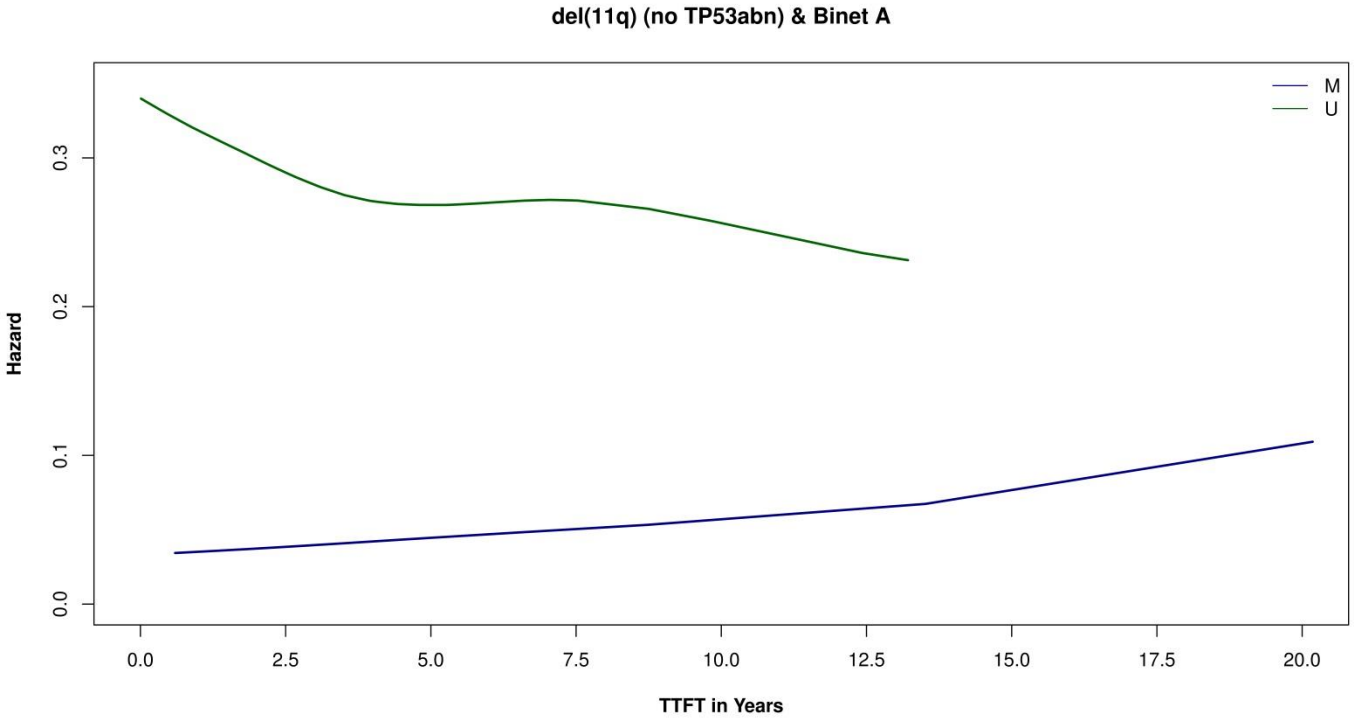
| U-CLL | | |
|---|---|---|
| **Time-points** | **P-value** | **Action** |
| 2.54 | 0.82 | Eliminated |
| 1.27 | 0.65 | Eliminated |
| 3.78 | 0.30 | Eliminated |
| 4.67 | 0.26 | Eliminated |
| 6.46 | 0.37 | Eliminated |

**Supplemental Figures 1-5:** A standard Kaplan-Meier survival plot and a hazard plot are displayed for all the subgroups considered (besides the entire cohort and cases with *TP53* aberrations [*TP53*abn, del(17p) and/or *TP53* mutations], already displayed in Figure 1). In particular, Sup. Figure 1 corresponds to del(11q), non *TP53*abn cases, Sup. Figure 2 to cases carrying trisomy 12 with no *TP53*abn, Sup. Figure 3 to del(13q)/normal FISH cases, Sup. Figure 4 to NOTCH1 mutations, and Sup. Figure 5 to SF3B1 mutations. The hazard plot shows the estimated proportion of patients who received treatment for the first time in a defined time interval, given that they were still treatment-free at the start of this interval. The p-value corresponding to the log-rank test for the comparison of the survival distributions is displayed in the survival plot. The table including the number of patients at risk, and the cumulative number of events/censoring, applies in both plots.

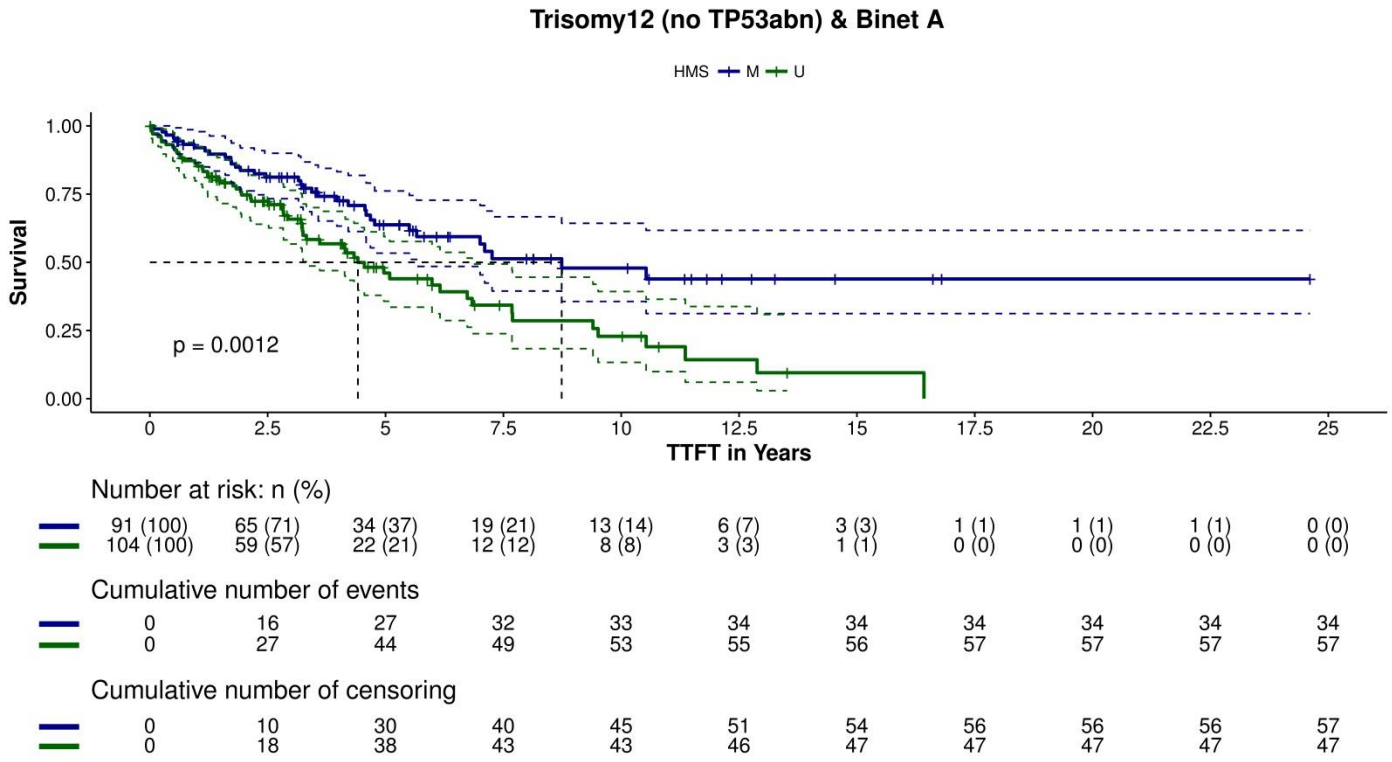
**S1A**


del(11q) (no TP53abn) & Binet A
HMS M U
Survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
2.5
5
7.5
10
12.5
15
17.5
20
TTFT in Years
Number at risk: n (%)
21 (100) 16 (76) 7 (33) 3 (14) 2 (10) 2 (10) 1 (5) 1 (5) 1 (5)
108 (100) 44 (41) 16 (15) 5 (5) 2 (2) 1 (1) 0 (0) 0 (0) 0 (0)
Cumulative number of events
0 1 3 4 4 4 4 4 4
0 57 75 83 86 86 87 87 87
Cumulative number of censoring
0 4 11 14 15 15 16 16 16
0 7 17 20 20 21 21 21 21

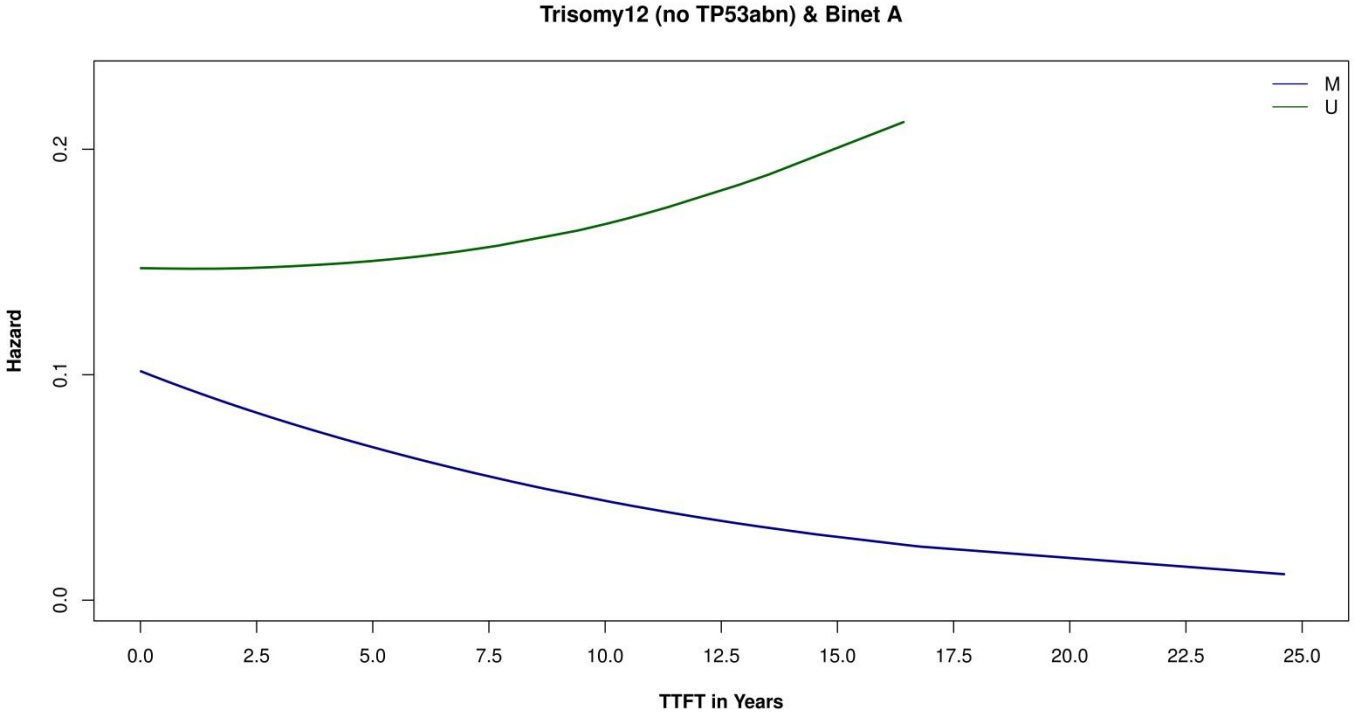
**S1B**


del(11q) (no TP53abn) & Binet A
M
U
Hazard
0.0
0.1
0.2
0.3
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
TTFT in Years

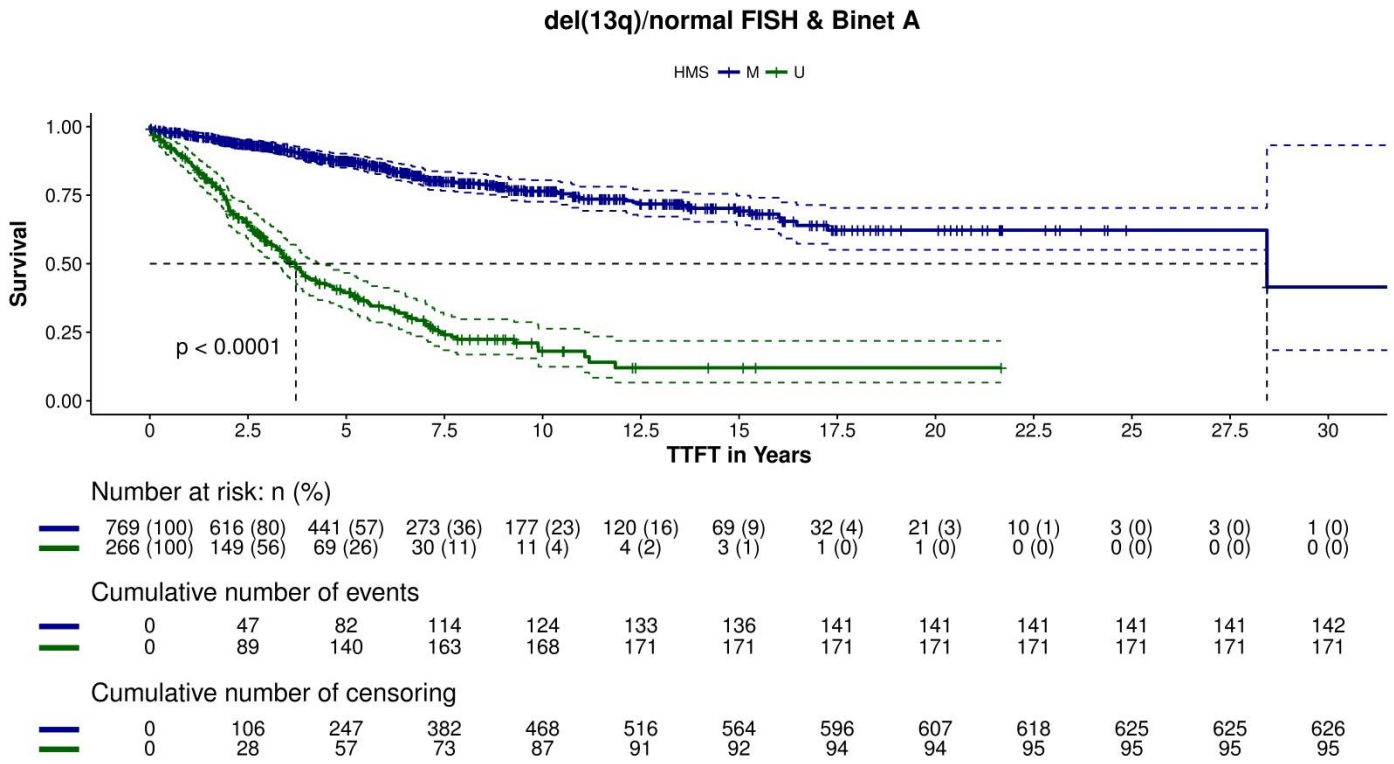
**S2A**


Trisomy12 (no TP53abn) & Binet A
HMS M U
Survival
1.00
0.75
0.50
0.25
0.00
p = 0.0012
0 2.5 5 7.5 10 12.5 15 17.5 20 22.5 25
TTFT in Years
Number at risk: n (%)
91 (100) 65 (71) 34 (37) 19 (21) 13 (14) 6 (7) 3 (3) 1 (1) 1 (1) 1 (1) 0 (0)
104 (100) 59 (57) 22 (21) 12 (12) 8 (8) 3 (3) 1 (1) 0 (0) 0 (0) 0 (0) 0 (0)
Cumulative number of events
0 16 27 32 33 34 34 34 34 34 34
0 27 44 49 53 55 56 57 57 57 57
Cumulative number of censoring
0 10 30 40 45 51 54 56 56 56 57
0 18 38 43 43 46 47 47 47 47 47

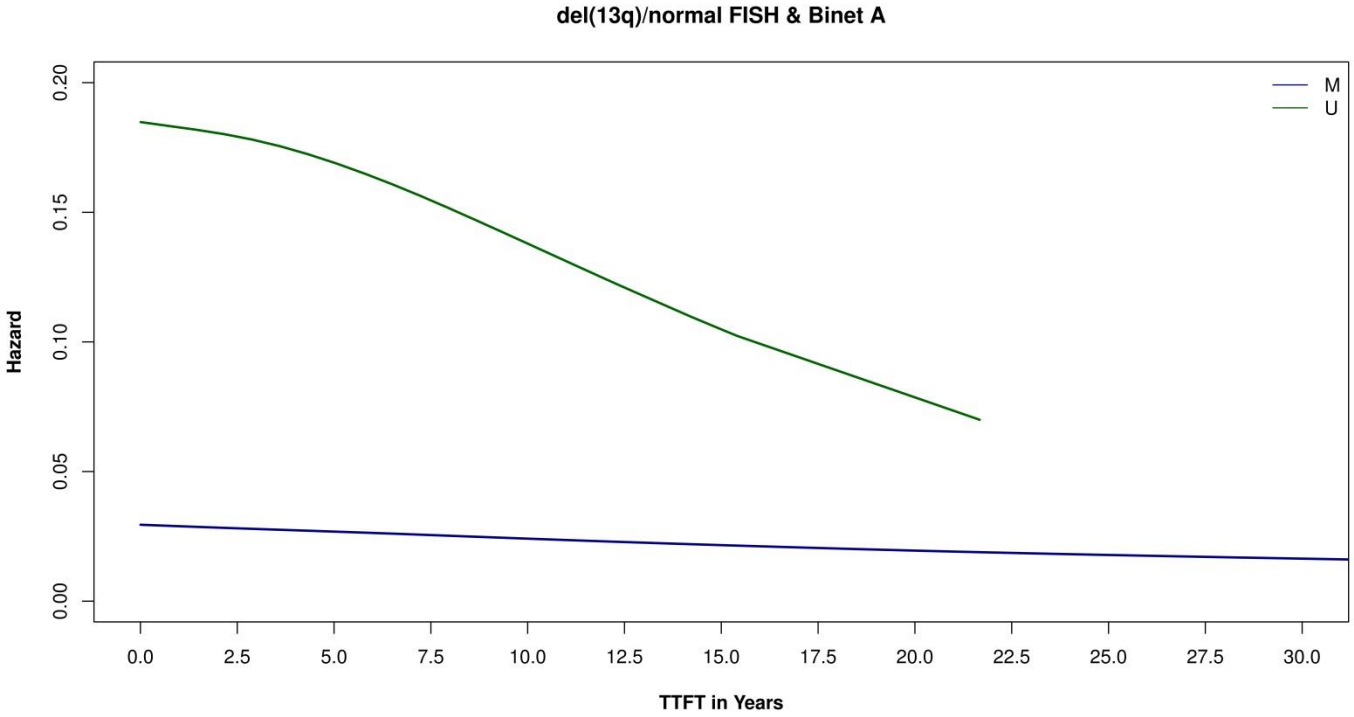
**S2B**


Trisomy12 (no TP53abn) & Binet A
M
U
Hazard
0.0
0.1
0.2
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0
TTFT in Years

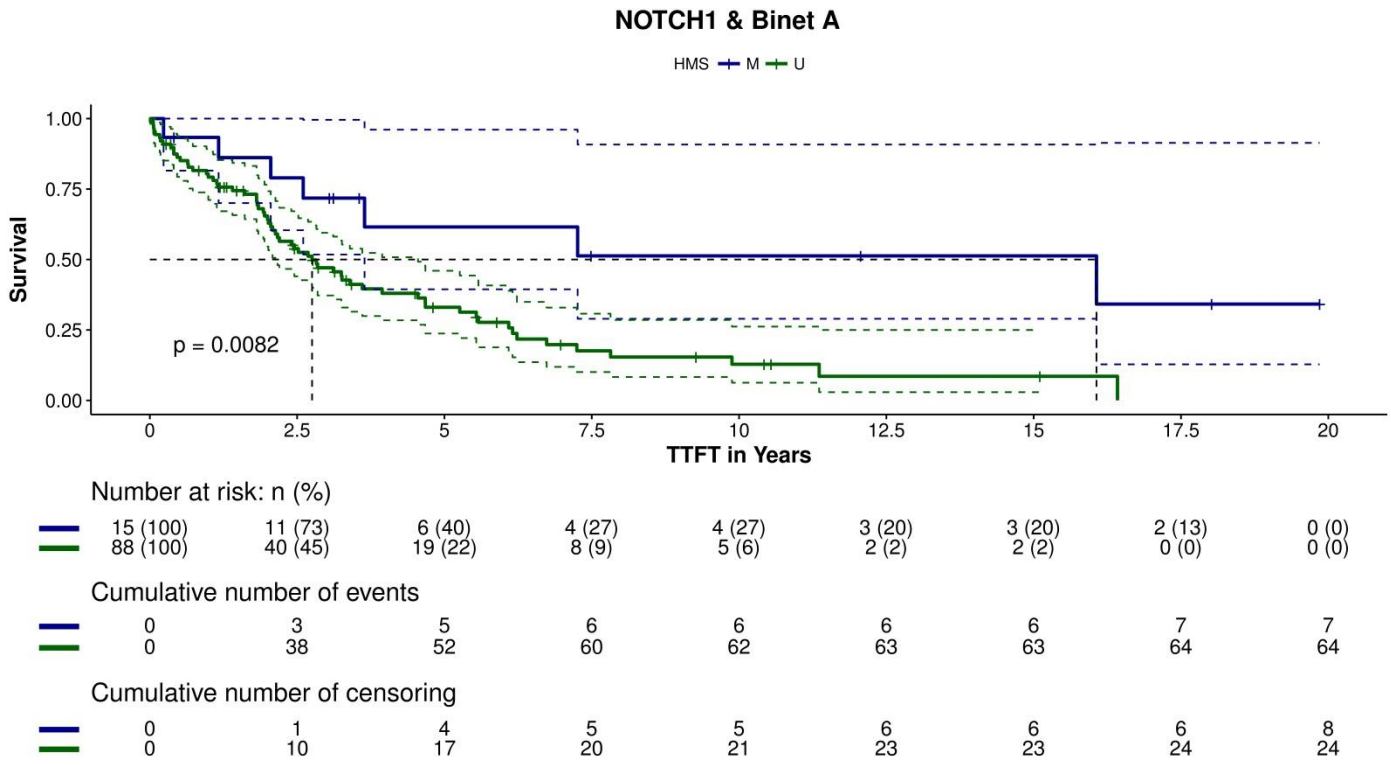
**S3A**


del(13q)/normal FISH & Binet A
HMS M U
Survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0 2.5 5 7.5 10 12.5 15 17.5 20 22.5 25 27.5 30
TTFT in Years
Number at risk: n (%)
769 (100) 616 (80) 441 (57) 273 (36) 177 (23) 120 (16) 69 (9) 32 (4) 21 (3) 10 (1) 3 (0) 3 (0) 1 (0)
266 (100) 149 (56) 69 (26) 30 (11) 11 (4) 4 (2) 3 (1) 1 (0) 1 (0) 0 (0) 0 (0) 0 (0) 0 (0)
Cumulative number of events
0 47 82 114 124 133 136 141 141 141 141 141 142
0 89 140 163 168 171 171 171 171 171 171 171 171
Cumulative number of censoring
0 106 247 382 468 516 564 596 607 618 625 625 626
0 28 57 73 87 91 92 94 94 95 95 95 95

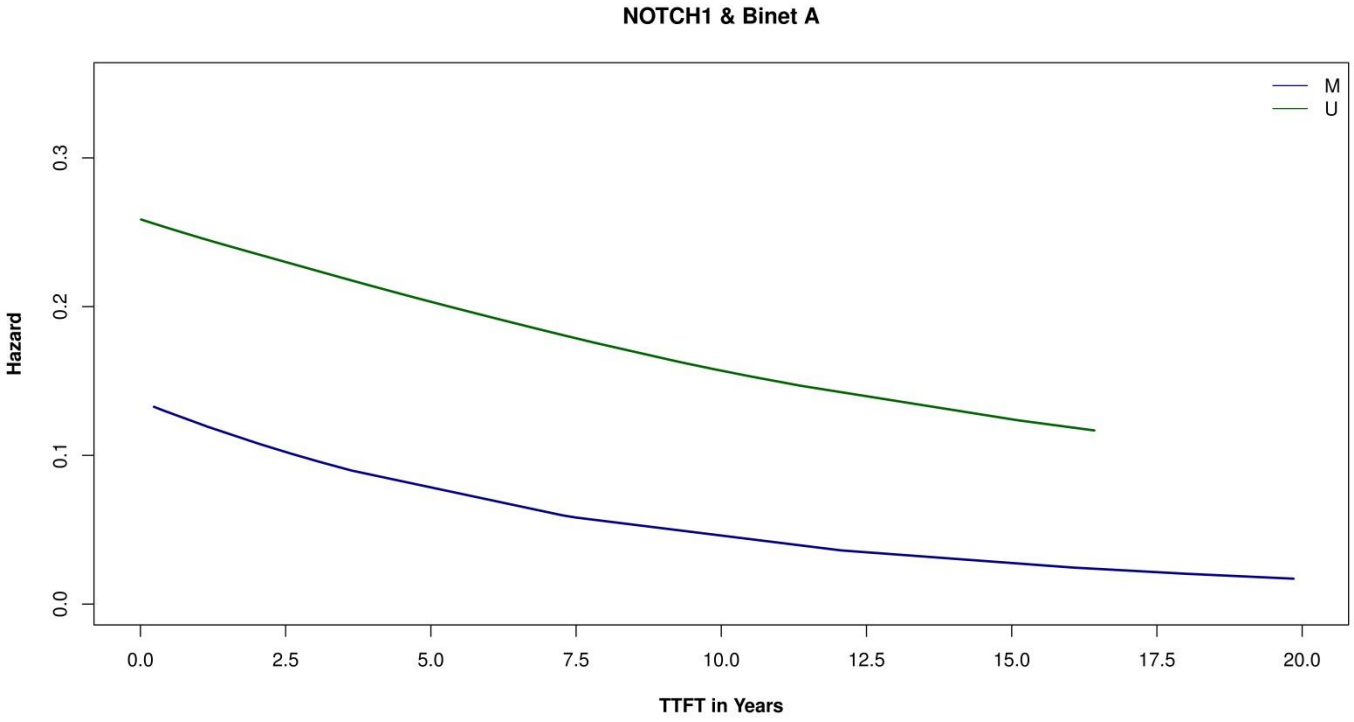
**S3B**


del(13q)/normal FISH & Binet A
M
U
Hazard
0.00
0.05
0.10
0.15
0.20
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0 27.5 30.0
TTFT in Years

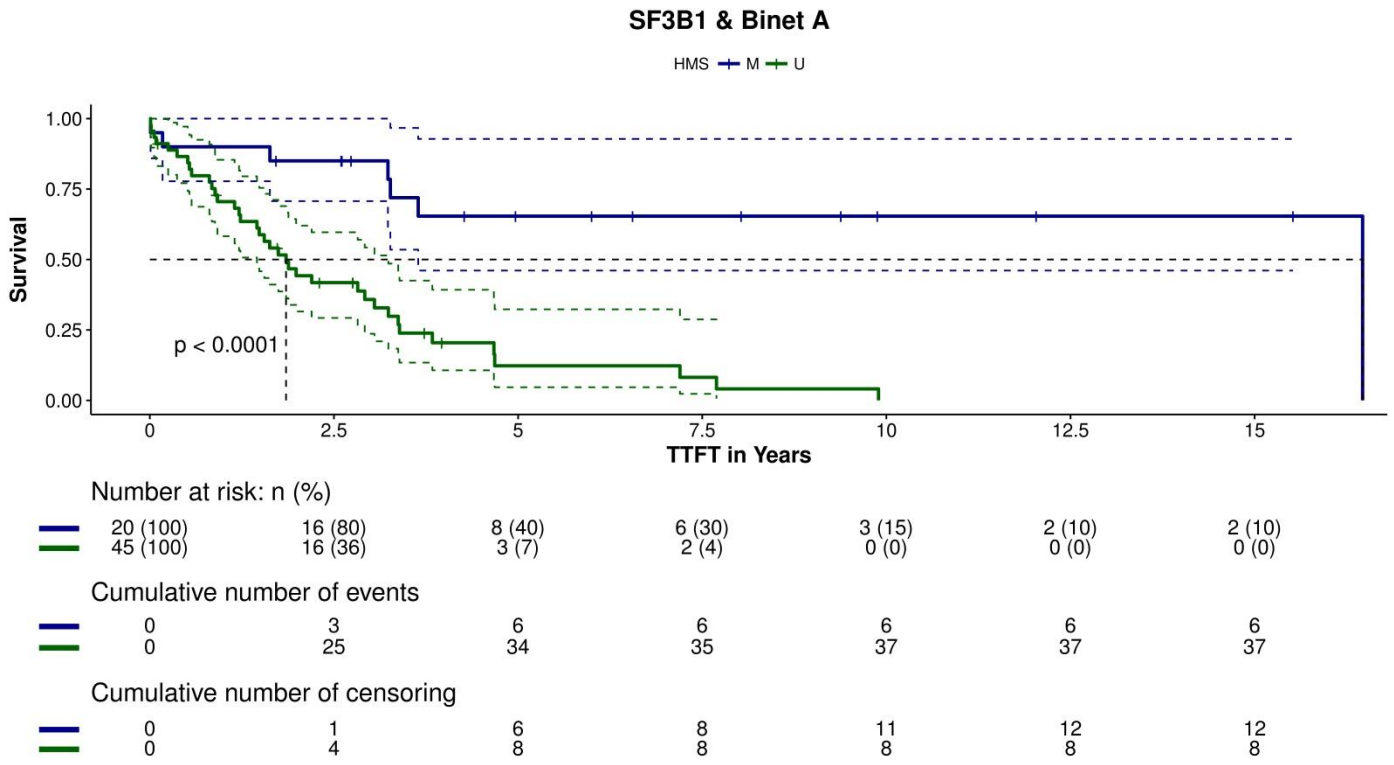
**S4A**


NOTCH1 & Binet A
HMS M U
Survival
1.00
0.75
0.50
0.25
0.00
p = 0.0082
0
2.5
5
7.5
10
12.5
15
17.5
20
TTFT in Years
Number at risk: n (%)
15 (100) 11 (73) 6 (40) 4 (27) 4 (27) 3 (20) 3 (20) 2 (13) 0 (0)
88 (100) 40 (45) 19 (22) 8 (9) 5 (6) 2 (2) 2 (2) 0 (0) 0 (0)
Cumulative number of events
0 3 5 6 6 6 6 7 7
0 38 52 60 62 63 63 64 64
Cumulative number of censoring
0 1 4 5 5 6 6 6 8
0 10 17 20 21 23 23 24 24

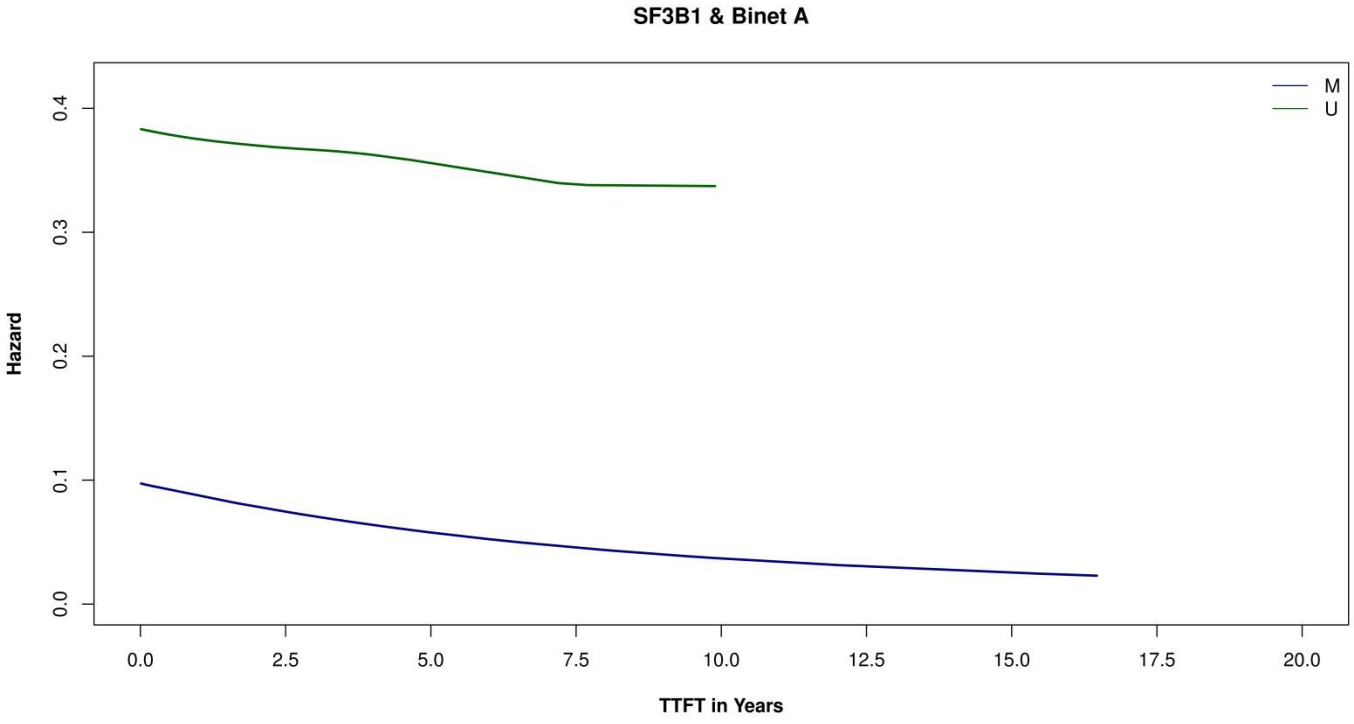
**S4B**


NOTCH1 & Binet A
M
U
Hazard
0.0
0.1
0.2
0.3
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
TTFT in Years

**S5A**

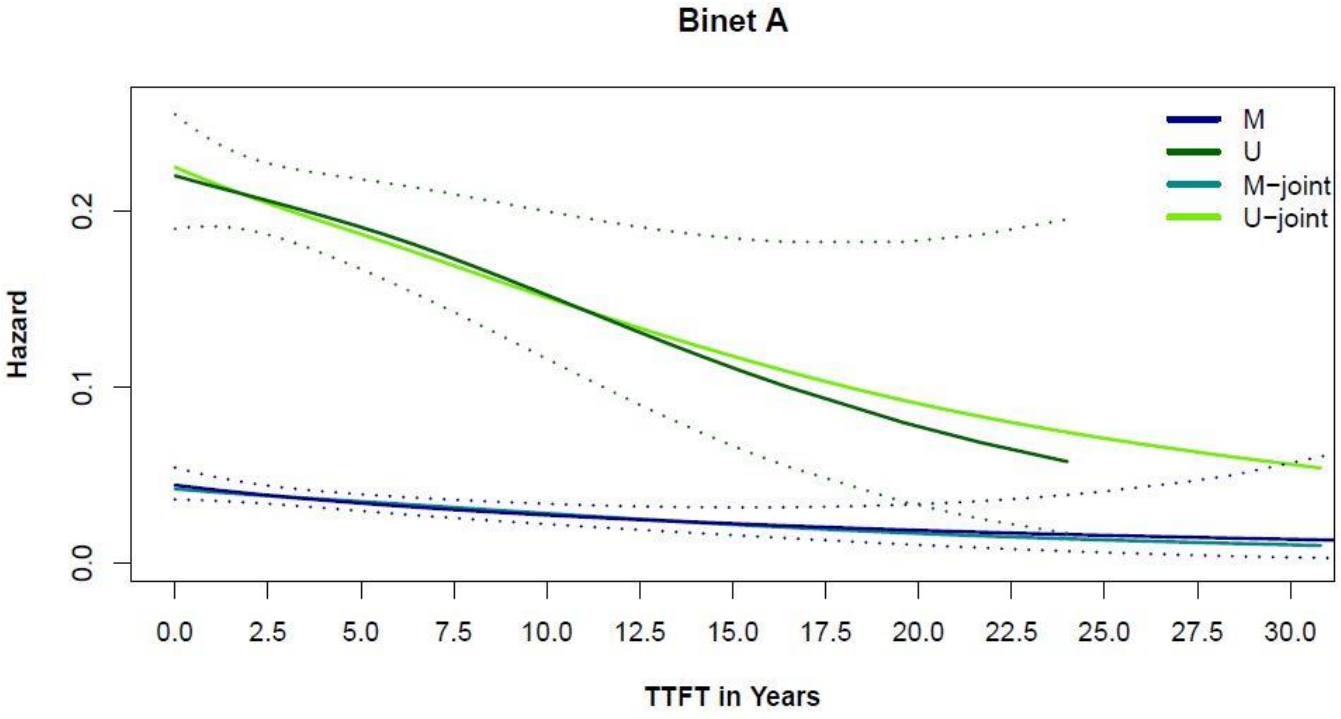

SF3B1 & Binet A
HMS M U
Survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
2.5
5
7.5
10
12.5
15
TTFT in Years
Number at risk: n (%)
20 (100) 16 (80) 8 (40) 6 (30) 3 (15) 2 (10) 2 (10)
45 (100) 16 (36) 3 (7) 2 (4) 0 (0) 0 (0) 0 (0)
Cumulative number of events
0 3 6 6 6 6 6
0 25 34 35 37 37 37
Cumulative number of censoring
0 1 6 8 11 12 12
0 4 8 8 8 8 8

**S5B**

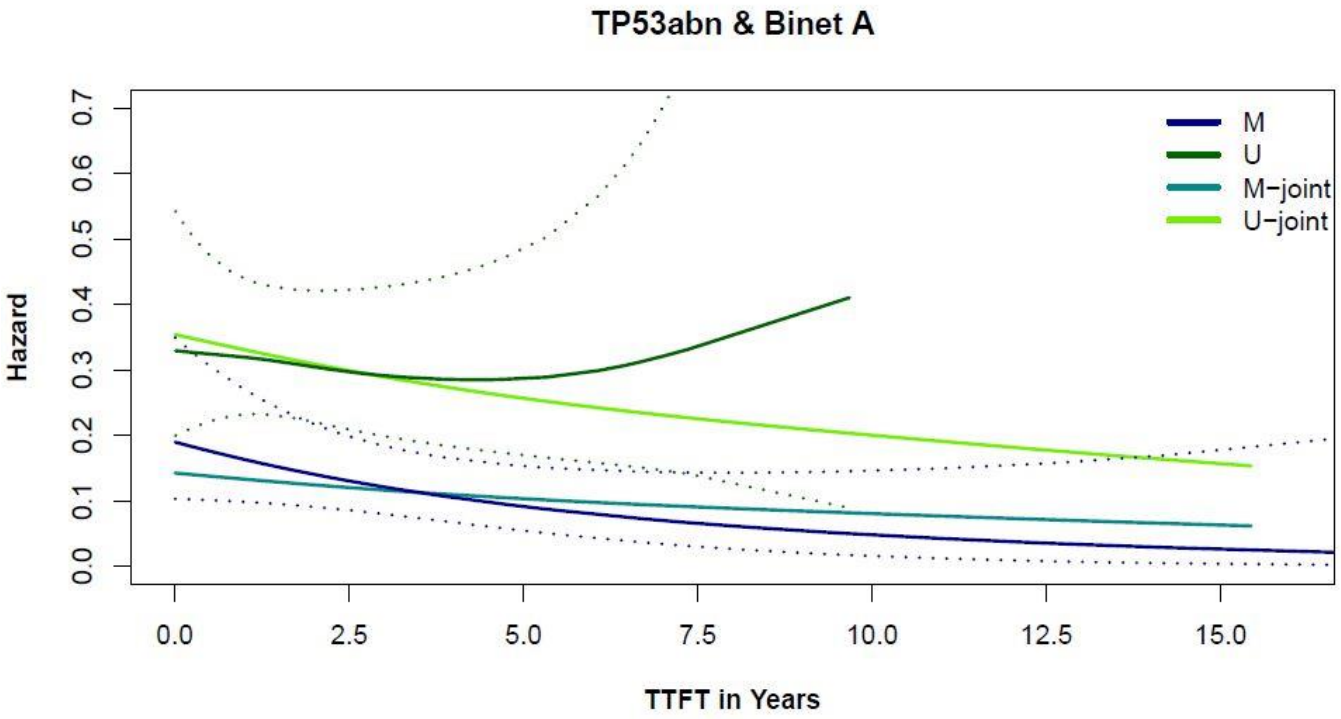

SF3B1 & Binet A
M
U
Hazard
0.4
0.3
0.2
0.1
0.0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
TTFT in Years

**Supplemental Figure 6:** A hazard plot is displayed for all the subgroups considered. In particular, S6A corresponds to the entire cohort, S6B to patients with *TP53* aberrations [*TP53*abn, del(17p) and/or *TP53* mutations], S6C to del(11q), non *TP53*abn cases, S6D to cases carrying trisomy 12 with no *TP53*abn, S6E to del(13q)/normal FISH cases, S6F to *NOTCH1* mutations, and S6G to *SF3B1* mutations. Each hazard plot displays the hazard curves developed separately for the M-CLL and the U-CLL patients (separate models), represented in the legend by M and U, respectively, with their 95% confidence intervals, and the corresponding hazard curves developed based on the joint adjusted model, represented in the legend by M-joint and U-joint, respectively. In the latter case the proportional hazards are assumed over-time. The joint model is displayed as a reference.

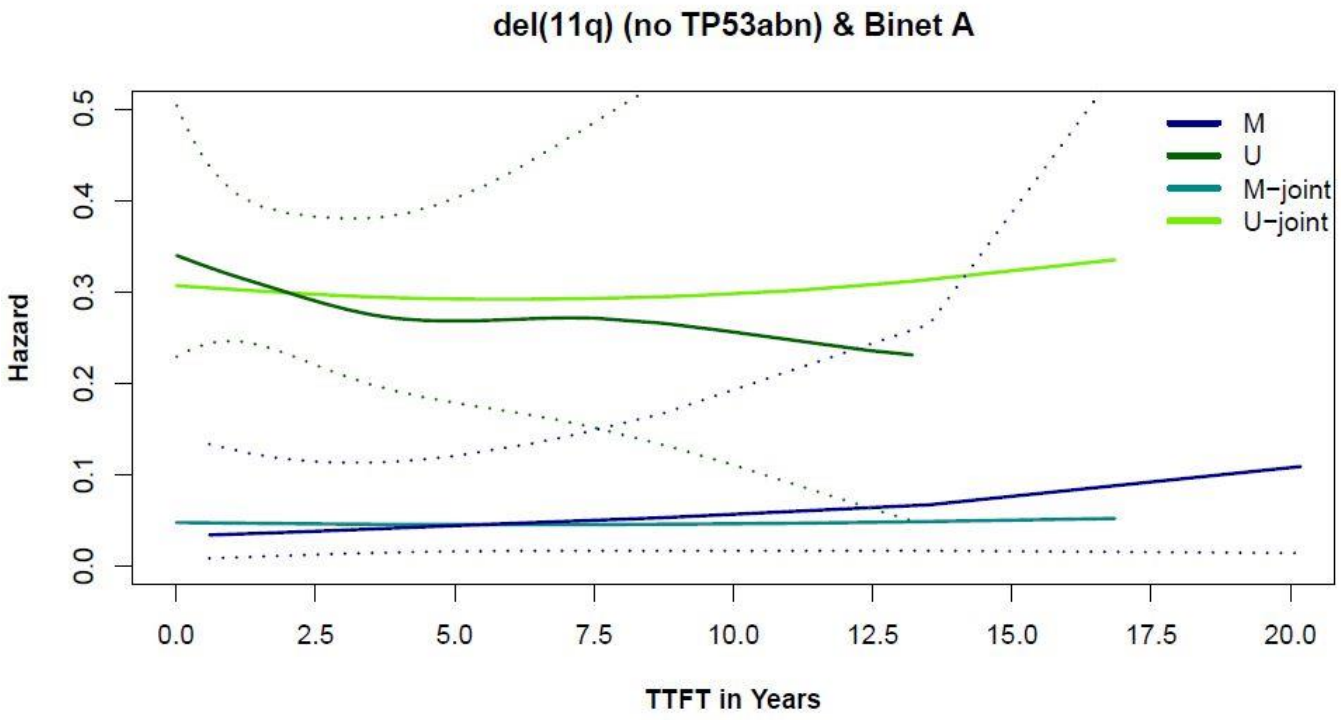
**S6A**



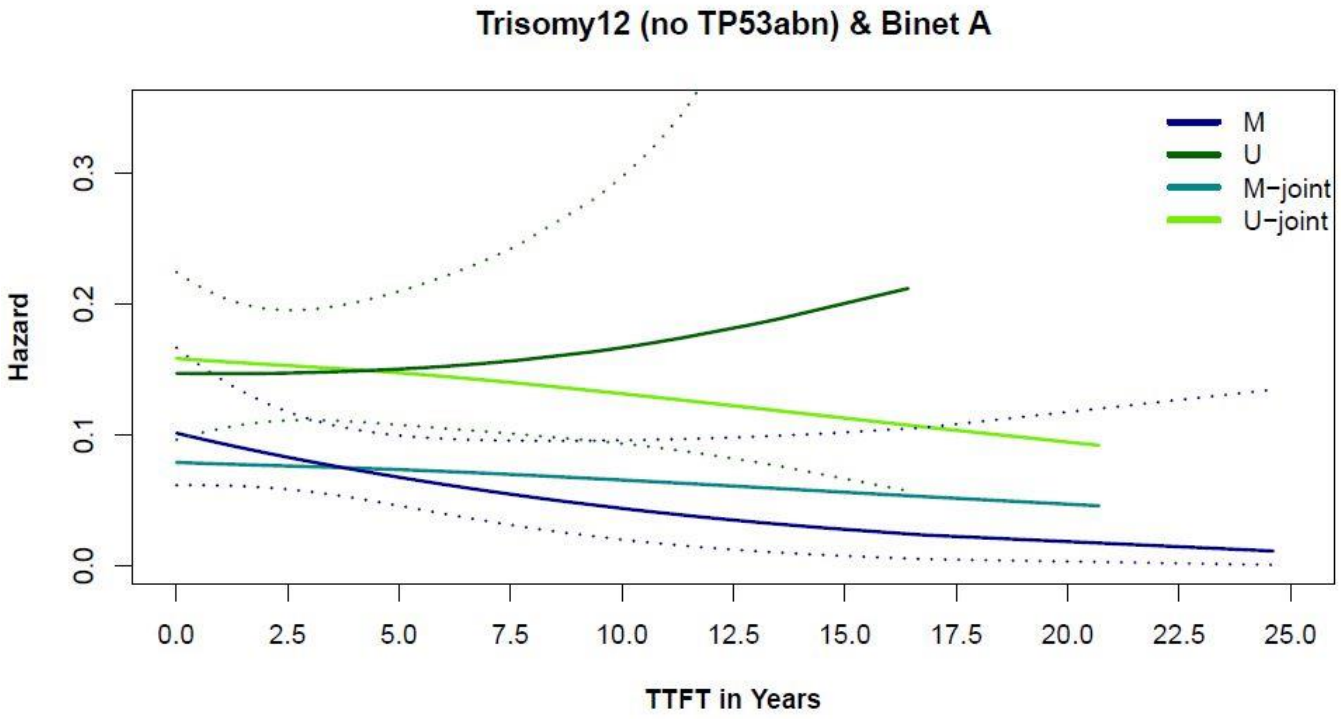
**S6B**


TP53abn & Binet A
Hazard
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.0
2.5
5.0
7.5
10.0
12.5
15.0
TTFT in Years
M
U
M−joint
U−joint

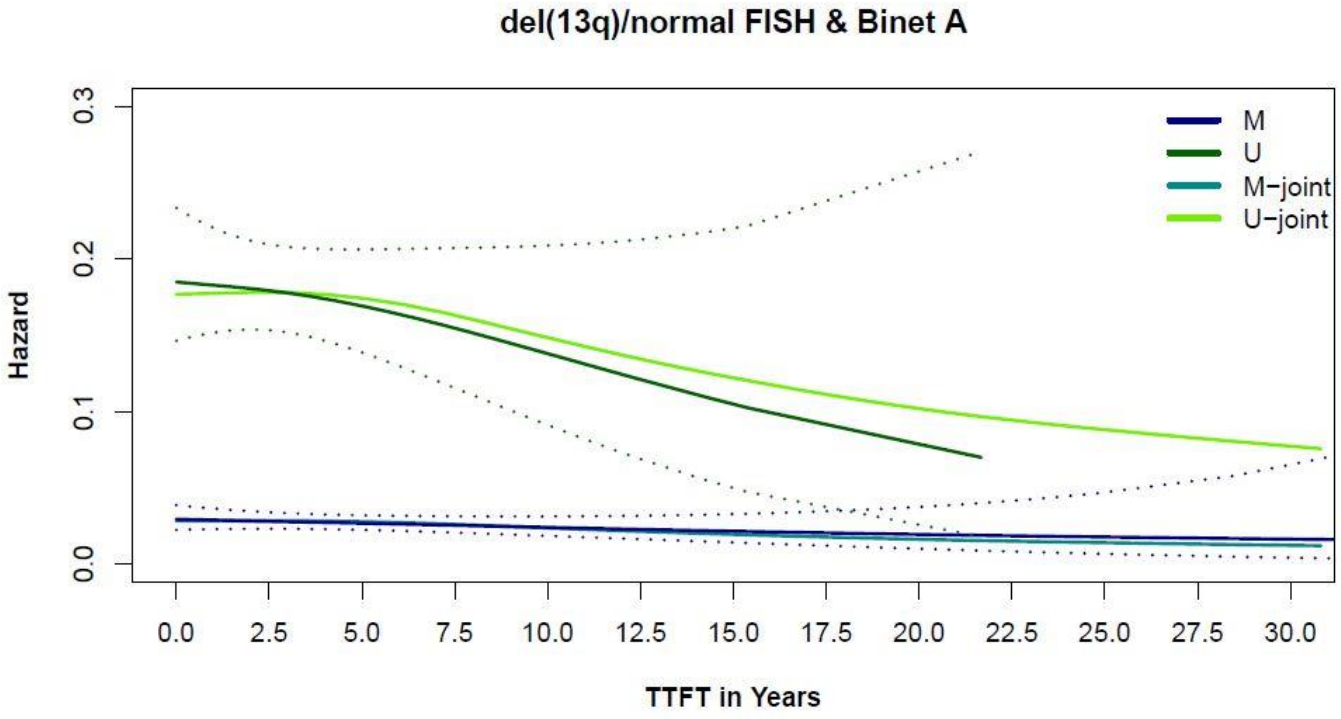
**S6C**


del(11q) (no TP53abn) & Binet A
Hazard
0.0
0.1
0.2
0.3
0.4
0.5
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
TTFT in Years
M
U
M−joint
U−joint

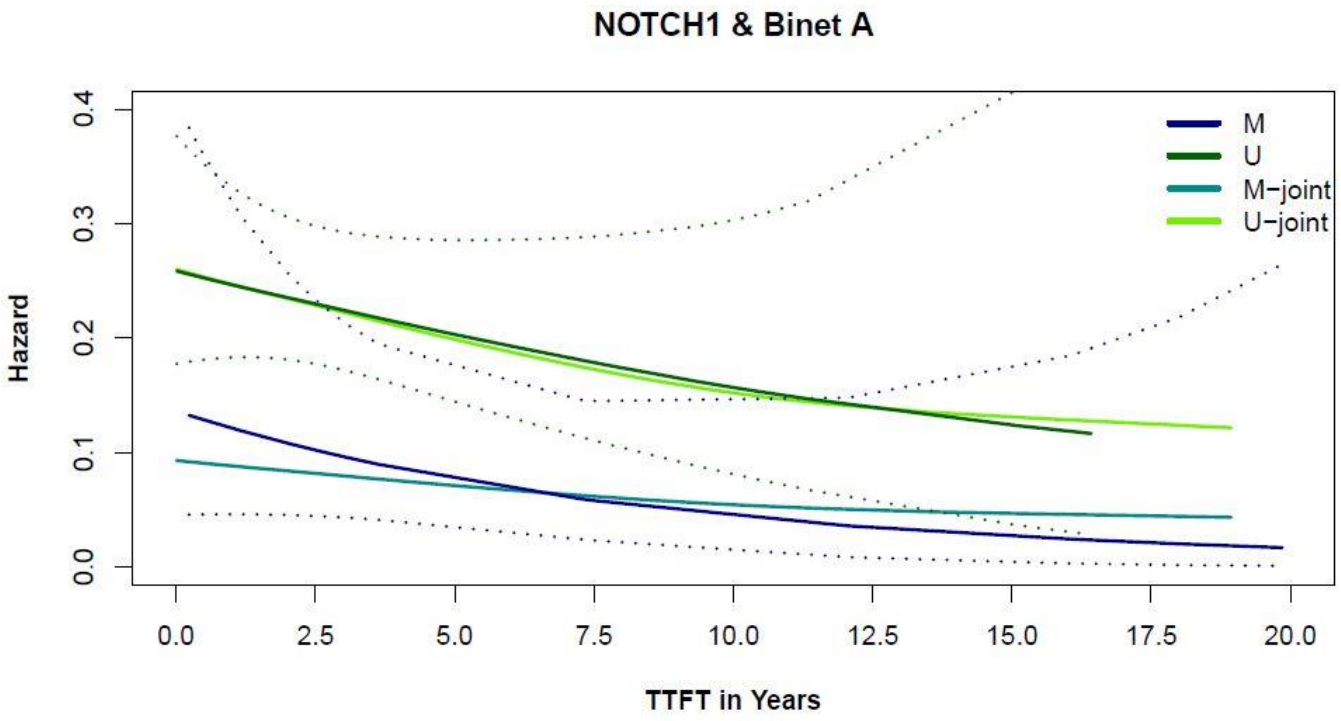
**S6D**


Trisomy12 (no TP53abn) & Binet A
M
U
M−joint
U−joint
Hazard
0.0
0.1
0.2
0.3
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
TTFT in Years

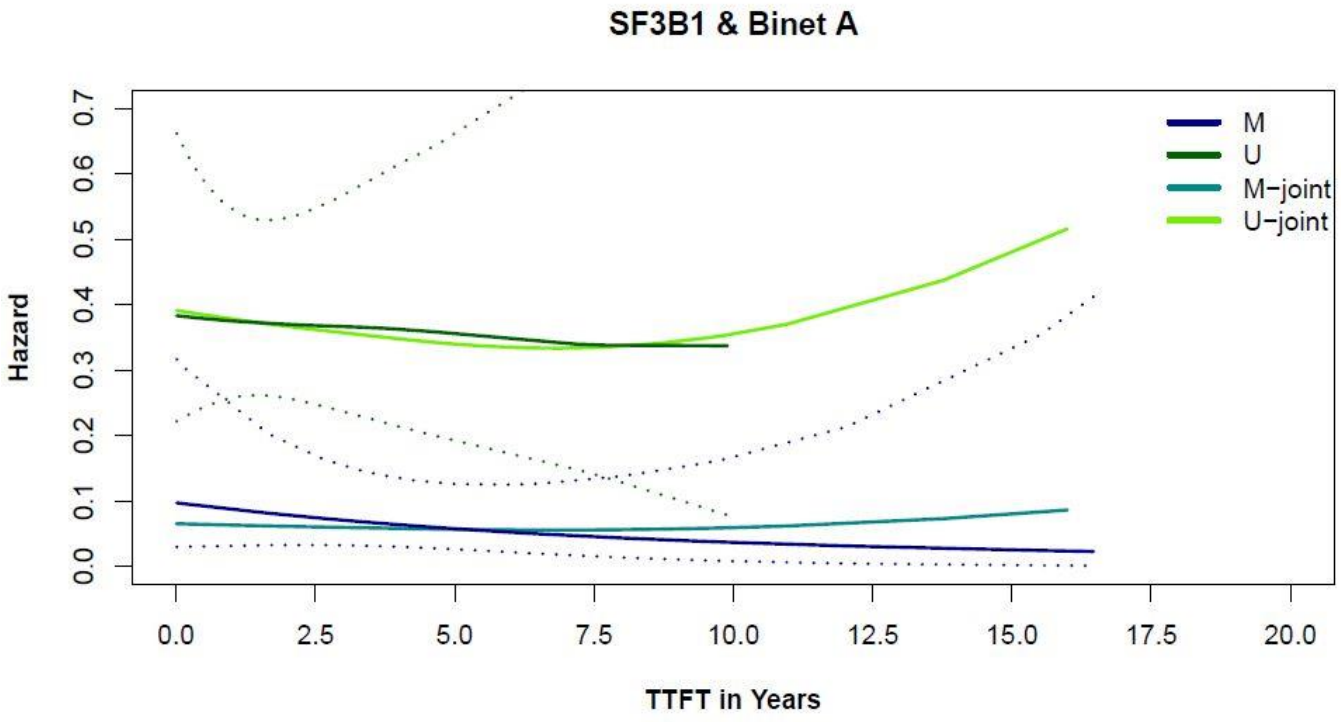
**S6E**


del(13q)/normal FISH & Binet A
M
U
M−joint
U−joint
Hazard
0.0
0.1
0.2
0.3
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
22.5
25.0
27.5
30.0
TTFT in Years

**S6F**

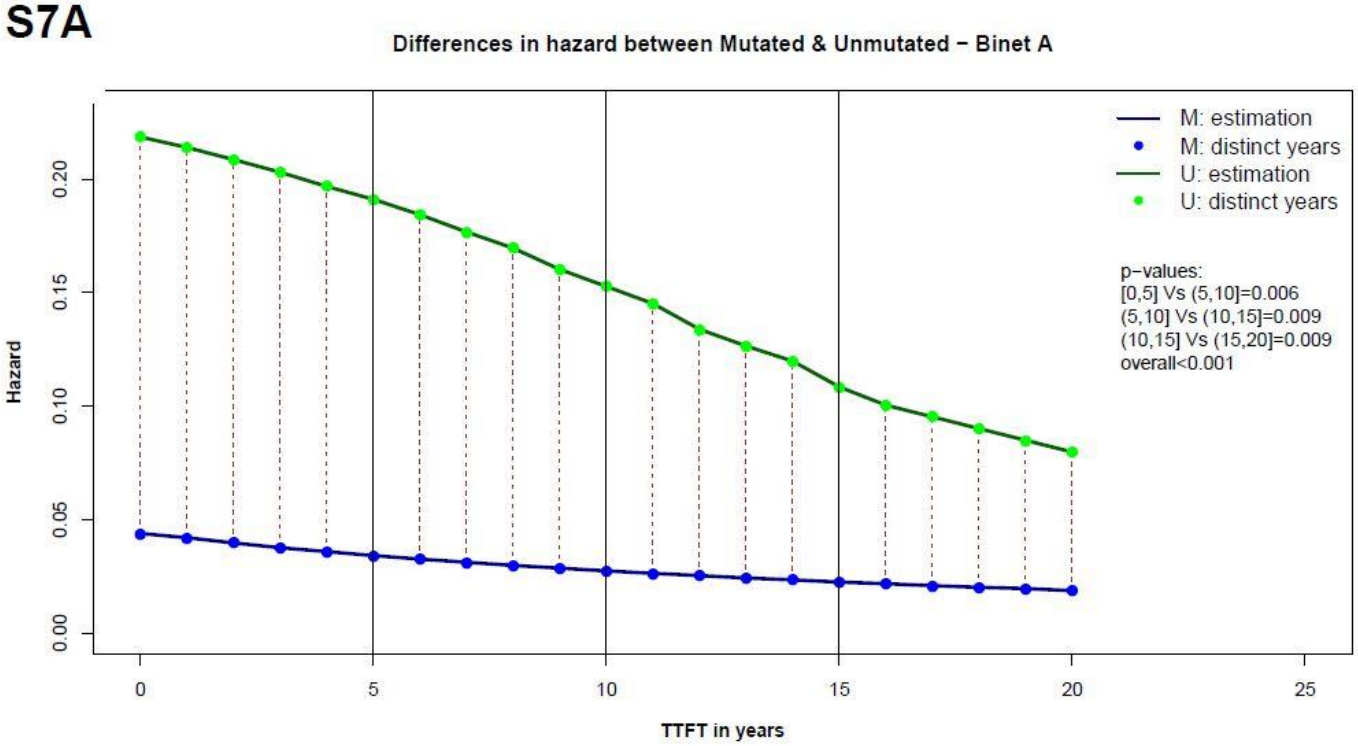

NOTCH1 & Binet A
Hazard
0.0
0.1
0.2
0.3
0.4
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
TTFT in Years
M
U
M−joint
U−joint

**S6G**

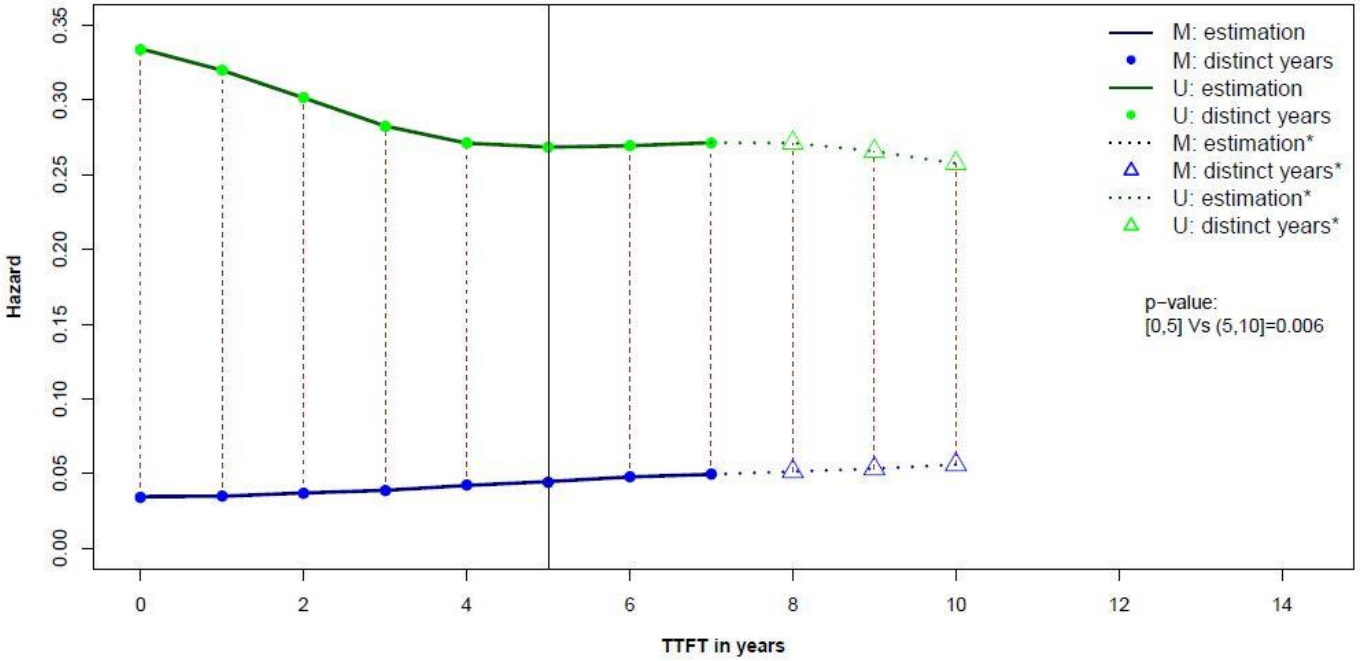

SF3B1 & Binet A
Hazard
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
TTFT in Years
M
U
M−joint
U−joint

**Supplemental Figure 7:** A hazard plot is displayed for all the subgroups considered (besides cases with *TP53* aberrations [*TP53*abn, del(17p) and/or *TP53* mutations], already displayed in Figure 2). In particular, S7A corresponds to the entire cohort, S7B to del(11q), non *TP53*abn cases, S7C to cases carrying trisomy 12 with no *TP53*abn, S7D to del(13q)/normal FISH cases, S7E to *NOTCH1* mutations, and S7F to *SF3B1* mutations. The hazard plot shows the estimated proportion of patients who received treatment for the first time in a defined time interval, given that they were still treatment-free at the start of this interval. The hazard differences between the curves for cases with mutated (M-CLL) and unmutated (U-CLL) IGHV genes are represented by vertical dashed lines. The p-values of the comparison within consecutive 5-year intervals of the distributions of hazard differences between M-CLL and U-CLL are also displayed. Based on the number of patients at risk and the number of events at different time-points, for some subgroups specific time-points were selected as landmarks and the hazard curves from those points and onwards (indicated by an asterisk) were dotted to indicate the small number of patients at risk and/or the small or inexistent number of events (see e.g. S7B).

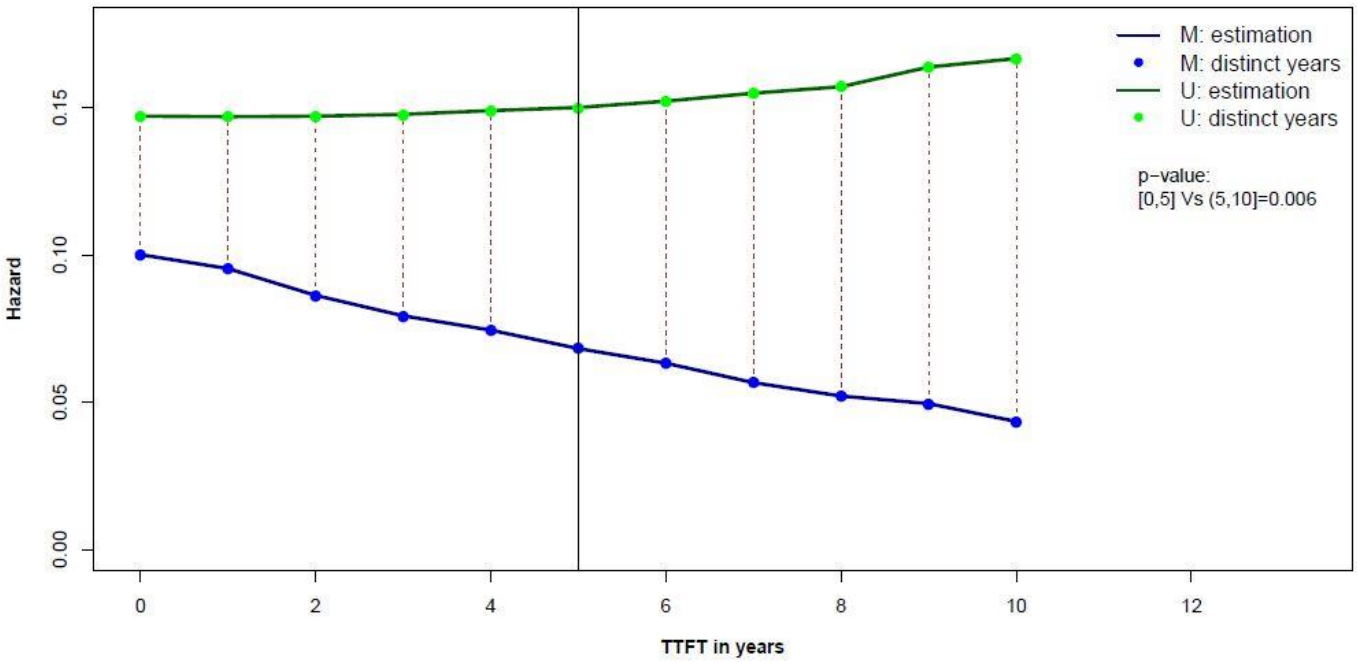
**S7A**


Differences in hazard between Mutated & Unmutated − Binet A
M: estimation
M: distinct years
U: estimation
U: distinct years
p−values:
[0,5] Vs (5,10]=0.006
(5,10] Vs (10,15]=0.009
(10,15] Vs (15,20]=0.009
overall<0.001
Hazard
0.00
0.05
0.10
0.15
0.20
0
5
10
15
20
25
TTFT in years

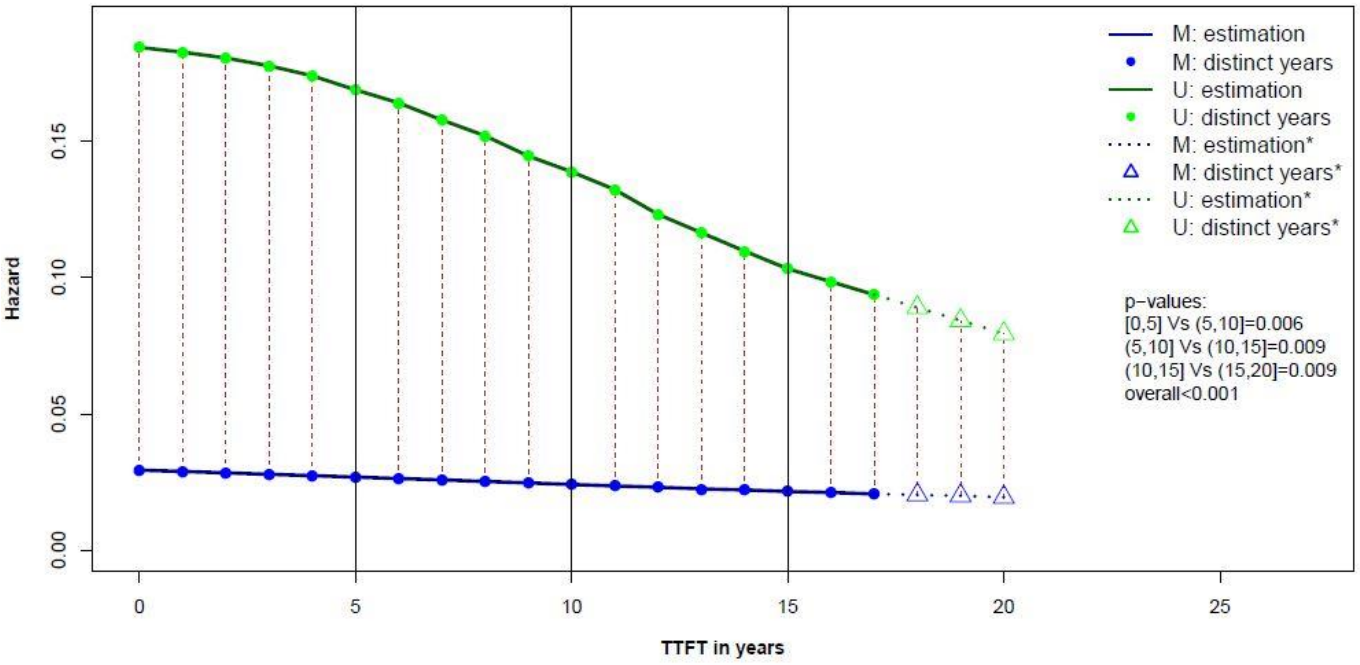
**S7B**


Differences in hazard between Mutated & Unmutated − del(11q) (no TP53abn) & Binet A
M: estimation
M: distinct years
U: estimation
U: distinct years
M: estimation*
M: distinct years*
U: estimation*
U: distinct years*
p−value:
[0,5] Vs (5,10]=0.006
Hazard
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0
2
4
6
8
10
12
14
TTFT in years

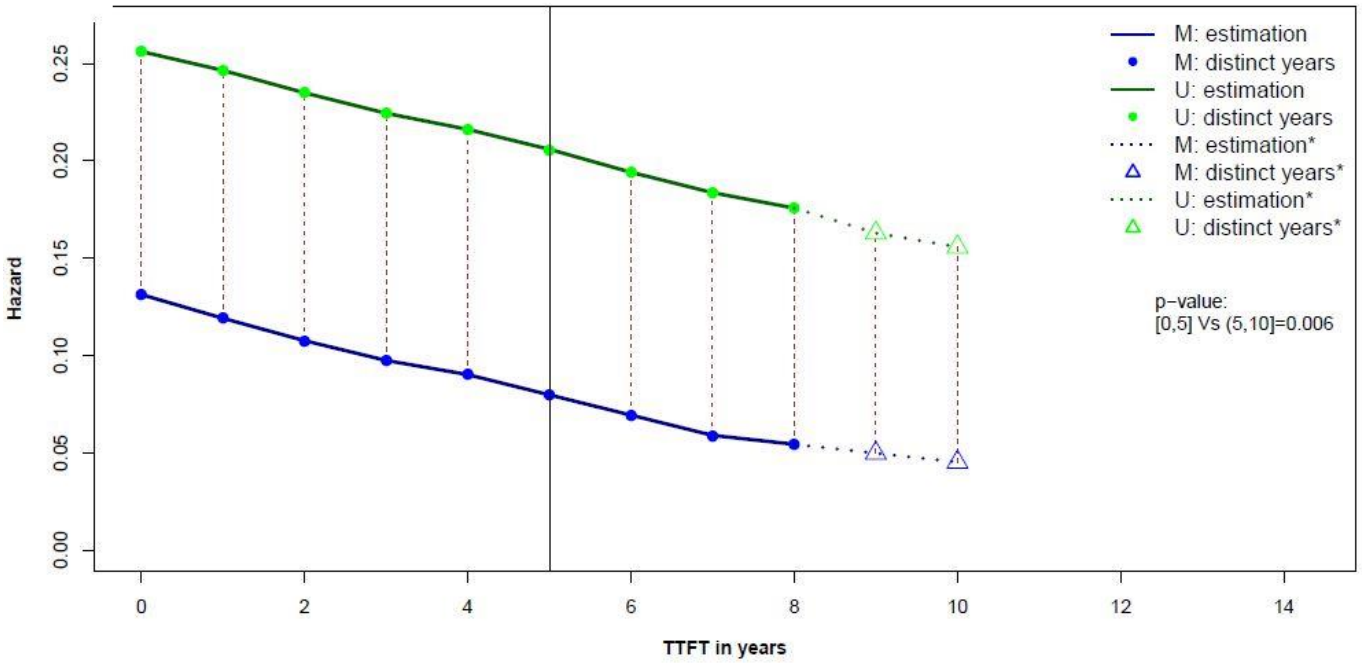
**S7C**


Differences in hazard between Mutated & Unmutated − Trisomy 12 (no TP53abn) & Binet A
M: estimation
M: distinct years
U: estimation
U: distinct years
p−value:
[0,5] Vs (5,10]=0.006
Hazard
0.00
0.05
0.10
0.15
0
2
4
6
8
10
12
TTFT in years

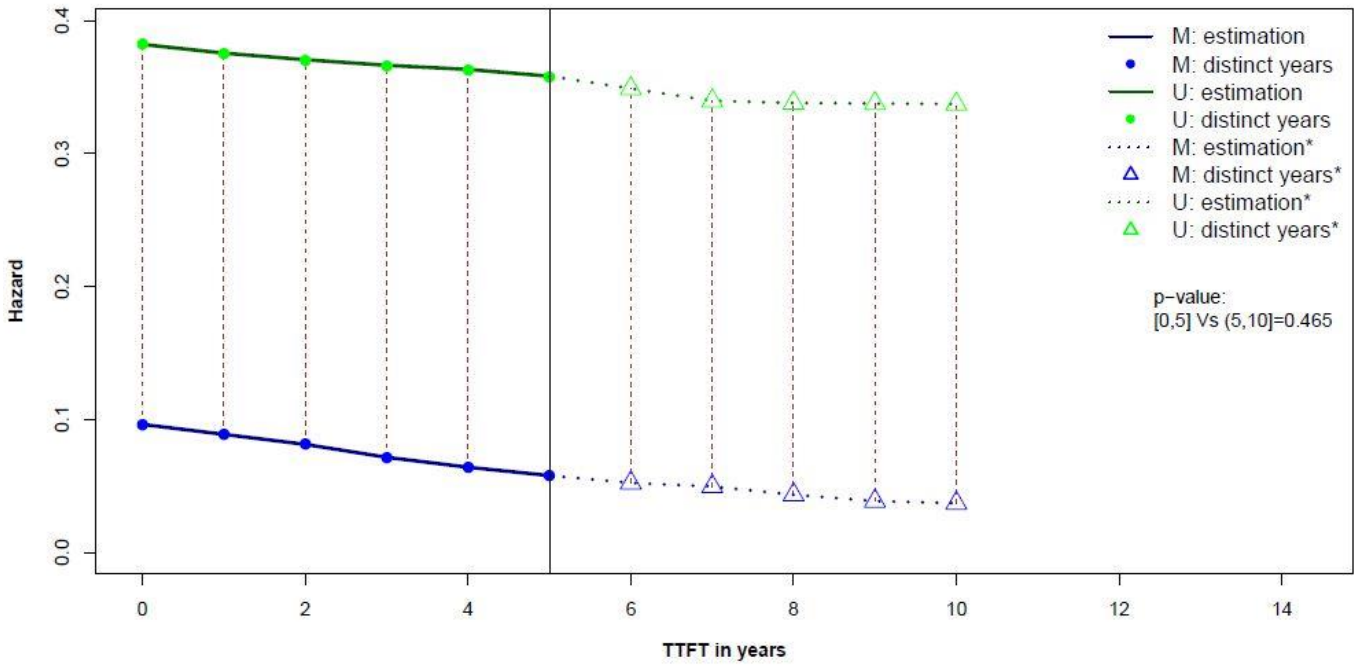
**S7D**


Differences in hazard between Mutated & Unmutated − del(13q)/normal FISH & Binet A
M: estimation
M: distinct years
U: estimation
U: distinct years
M: estimation*
M: distinct years*
U: estimation*
U: distinct years*
p−values:
[0,5] Vs (5,10]=0.006
(5,10] Vs (10,15]=0.009
(10,15] Vs (15,20]=0.009
overall<0.001
Hazard
0.00
0.05
0.10
0.15
0
5
10
15
20
25
TTFT in years

**S7E**


Differences in hazard between Mutated & Unmutated − NOTCH1 & Binet A
Hazard
0.00
0.05
0.10
0.15
0.20
0.25
0
2
4
6
8
10
12
14
TTFT in years
M: estimation
M: distinct years
U: estimation
U: distinct years
M: estimation*
M: distinct years*
U: estimation*
U: distinct years*
p−value:
[0,5] Vs (5,10]=0.006

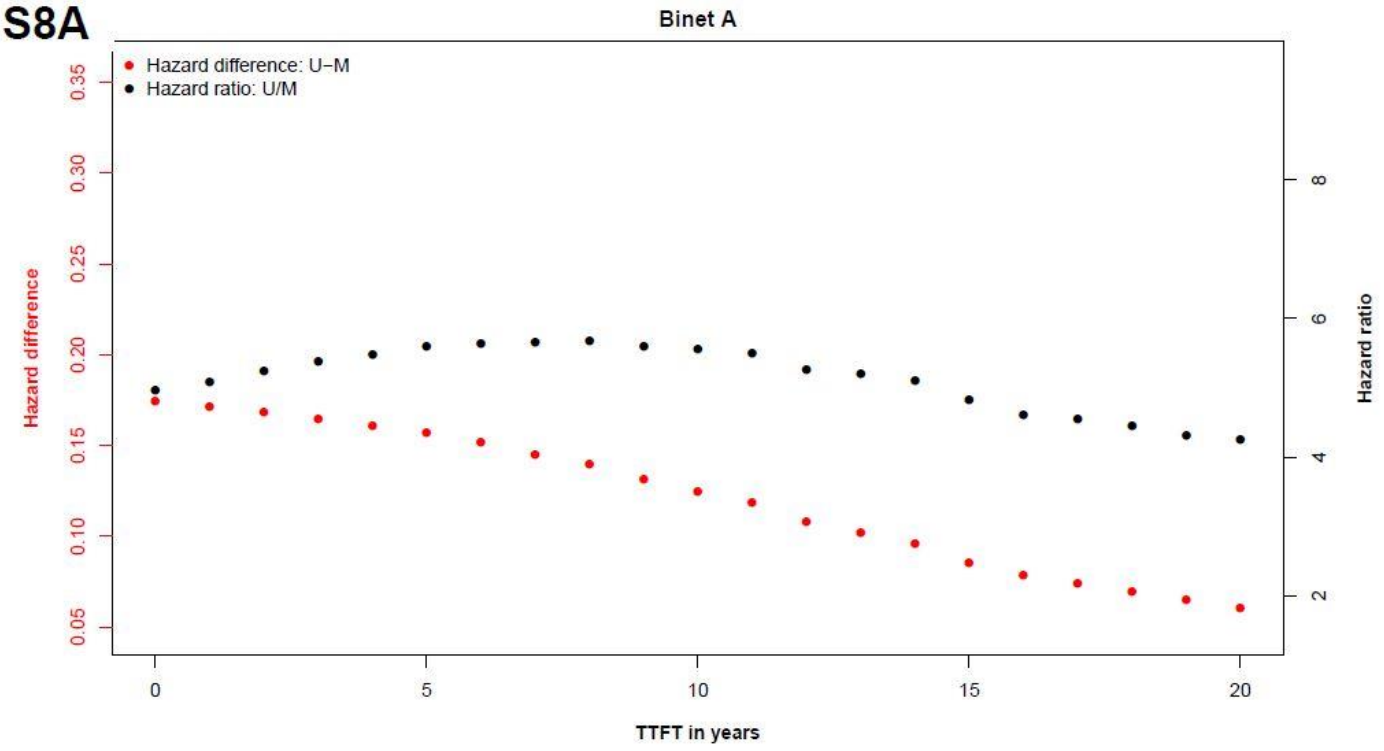
**S7F**


Differences in hazard between Mutated & Unmutated − SF3B1 & Binet A
Hazard
0.0
0.1
0.2
0.3
0.4
0
2
4
6
8
10
12
14
TTFT in years
M: estimation
M: distinct years
U: estimation
U: distinct years
M: estimation*
M: distinct years*
U: estimation*
U: distinct years*
p−value:
[0,5] Vs (5,10]=0.465

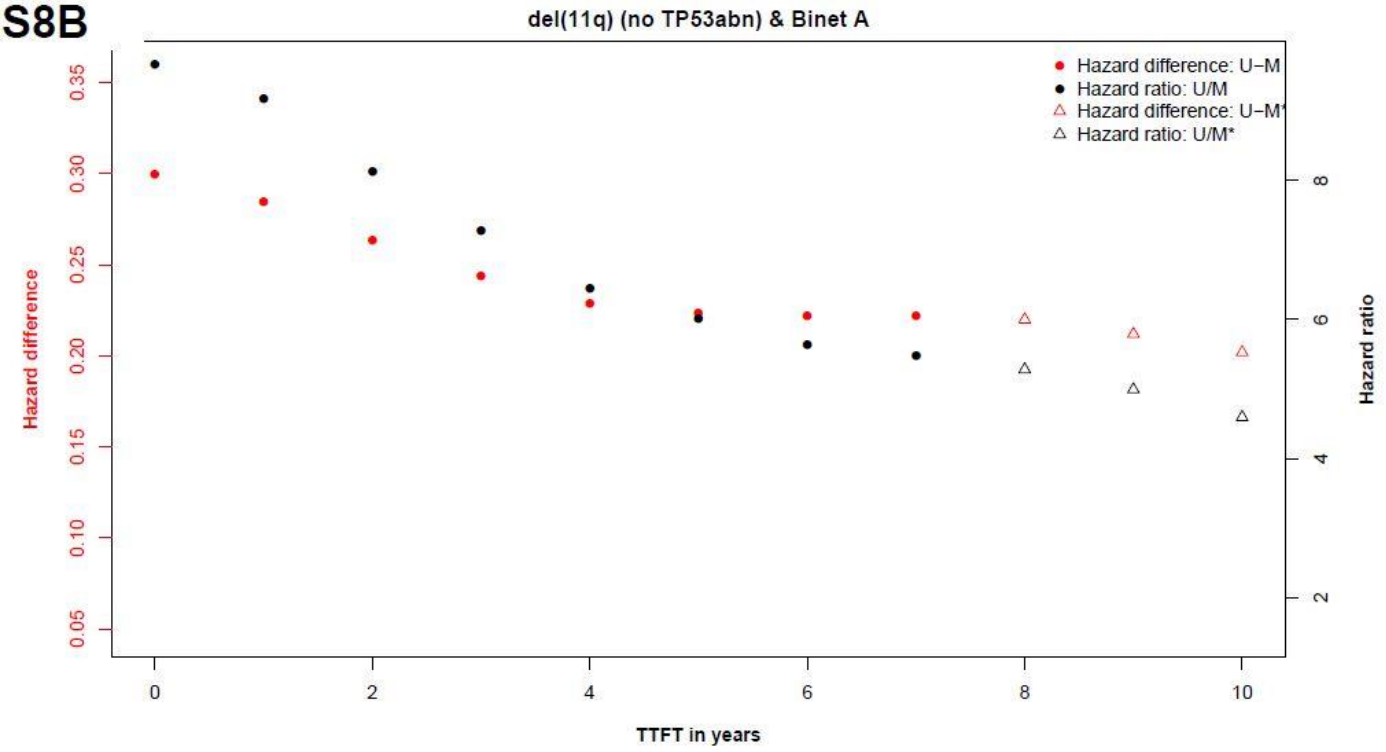
**Supplemental Figure 8:** The evolution of the hazard difference, U-CLL – M-CLL, with its scale displayed in the left vertical axis in red, and the evolution of the hazard ratio, U-CLL/M-CLL, with its scale displayed in the right vertical axis in black, are simultaneously displayed for all subgroups considered (apart *TP53*abn, already displayed in Figure 2). In particular, S8A corresponds to the entire cohort, S8B to del(11q), non *TP53*abn cases, S8C to cases carrying trisomy 12 with no *TP53*abn, S8D to del(13q)/normal FISH cases, S8E to *NOTCH1* mutations, and S8F to *SF3B1* mutations. The variation of each line represents the trend of the hazard differences and of the respective hazard ratios. A parallel line in either case would indicate stable difference or stable ratio over-time, respectively. Thus, this visualization enables to easily follow the evolution pattern of hazard comparison between M-CLL and U-CLL patients for each subgroup considered. Subsequently, such a visualization could aid in detecting critical time-points when assessing the comparison of hazard evolution between two groups of patients in the same way that the hazard plot could aid in detecting critical time-points when assessing the hazard evolution for a specific group of patients.

Based on the number of patients at risk and the number of events at different time-points, for some subgroups specific time-points were selected as landmarks and the bullets from those points and onwards (indicated by an asterisk) were replaced by triangles to indicate the small number of patients at risk and/or the small or inexistent number of events. All plots are given in the same scale for both the left and the right vertical axis to enable straightforward comparison between the subgroups.

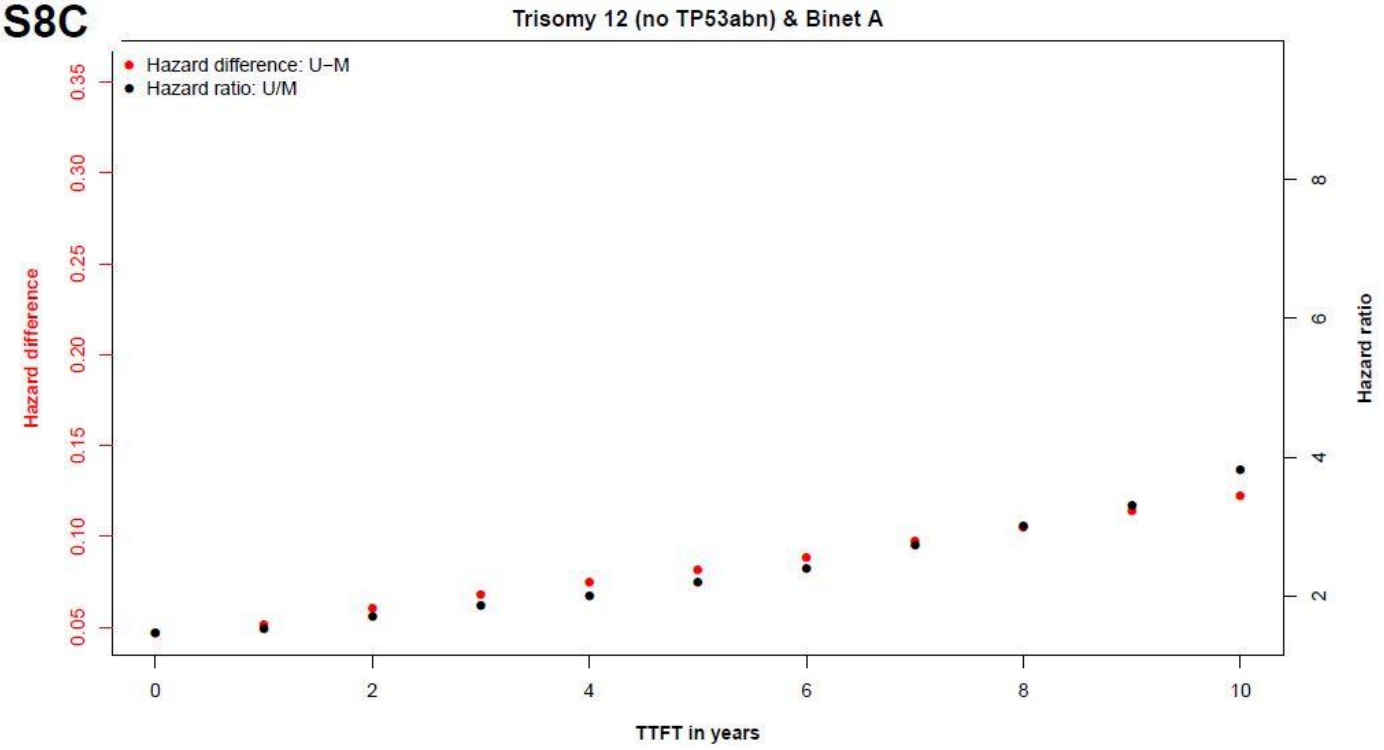
**S8A**


Binet A
Hazard difference: U−M
Hazard ratio: U/M
Hazard difference
Hazard ratio
TTFT in years
0.05
0.10
0.15
0.20
0.25
0.30
0.35
2
4
6
8
0
5
10
15
20

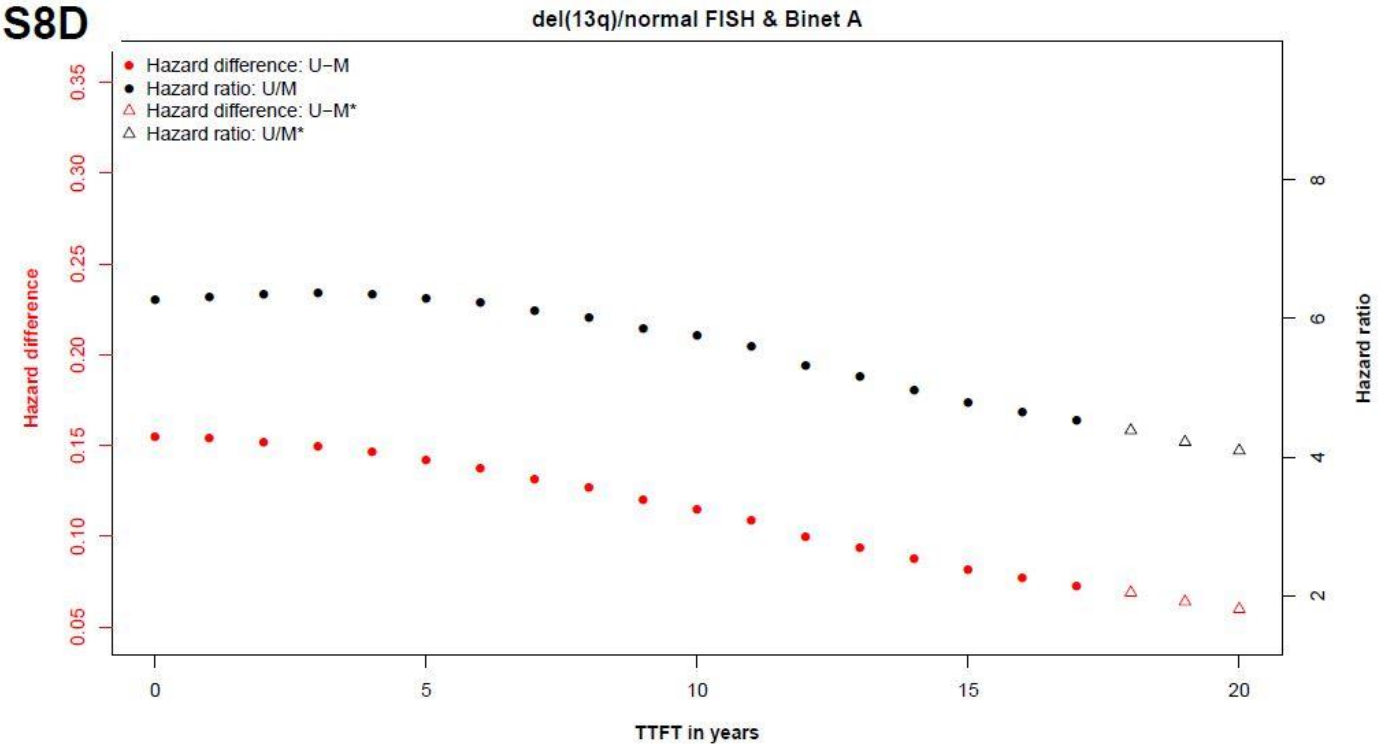
**S8B**


del(11q) (no TP53abn) & Binet A
Hazard difference: U−M
Hazard ratio: U/M
Hazard difference: U−M*
Hazard ratio: U/M*
Hazard difference
Hazard ratio
TTFT in years
0.05
0.10
0.15
0.20
0.25
0.30
0.35
2
4
6
8
0
2
4
6
8
10

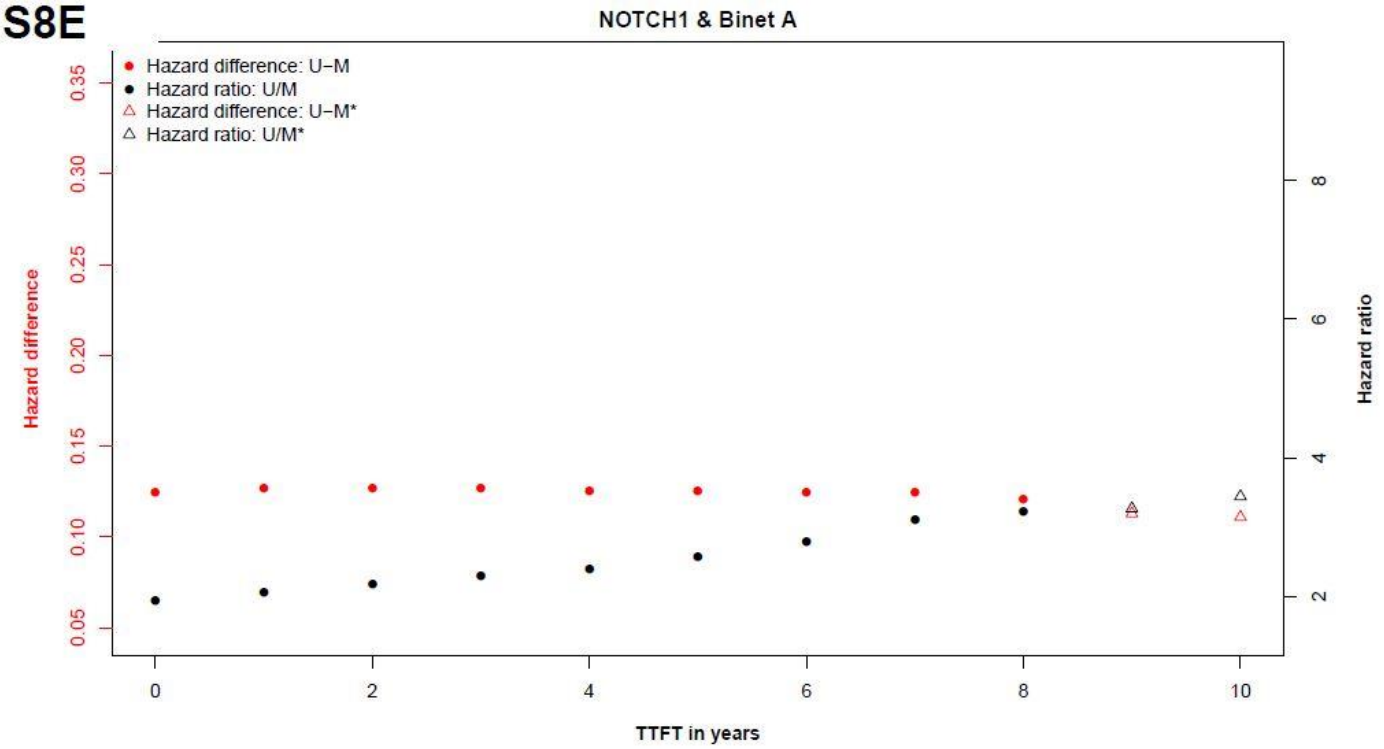
**S8C**


Trisomy 12 (no TP53abn) & Binet A
Hazard difference: U−M
Hazard ratio: U/M
Hazard difference
Hazard ratio
0.05
0.10
0.15
0.20
0.25
0.30
0.35
2
4
6
8
0
2
4
6
8
10
TTFT in years

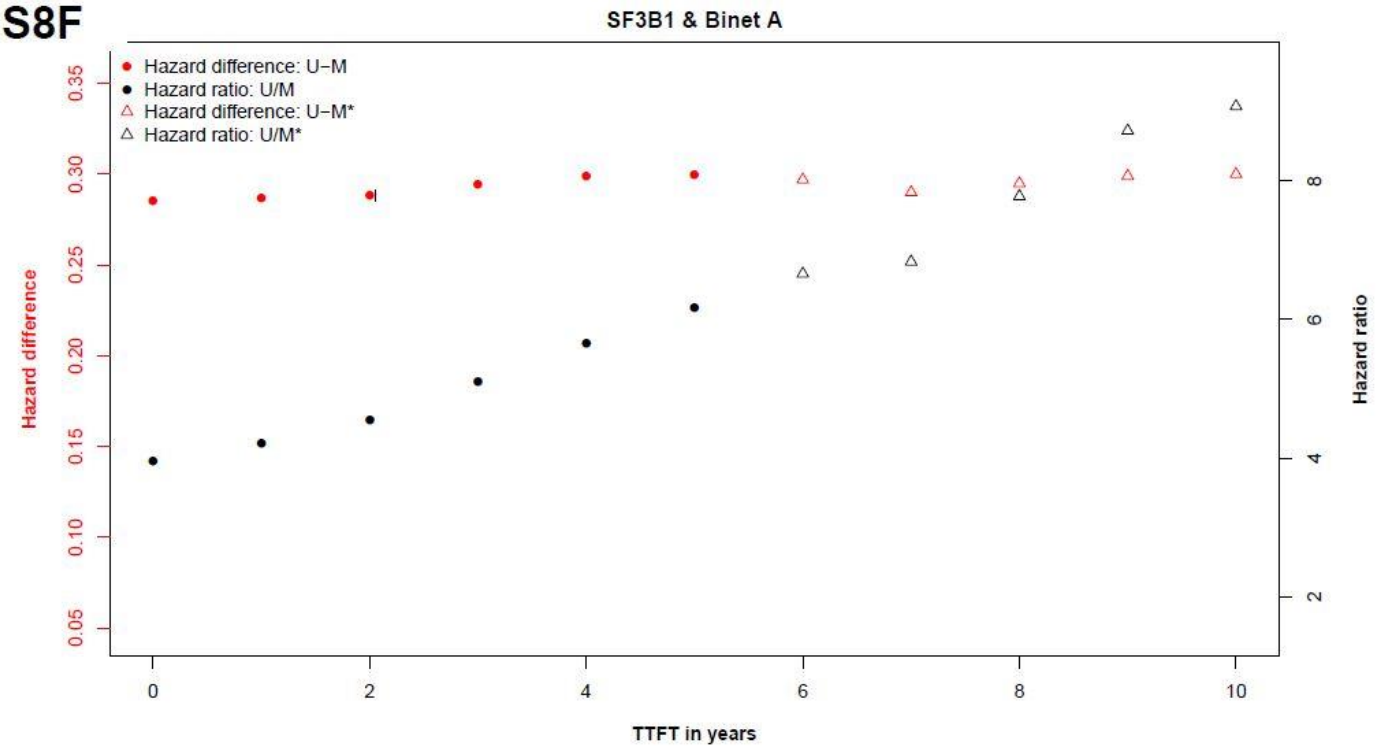
**S8D**


del(13q)/normal FISH & Binet A
Hazard difference: U−M
Hazard ratio: U/M
Hazard difference: U−M*
Hazard ratio: U/M*
Hazard difference
Hazard ratio
0.05
0.10
0.15
0.20
0.25
0.30
0.35
2
4
6
8
0
5
10
15
20
TTFT in years

**S8E**

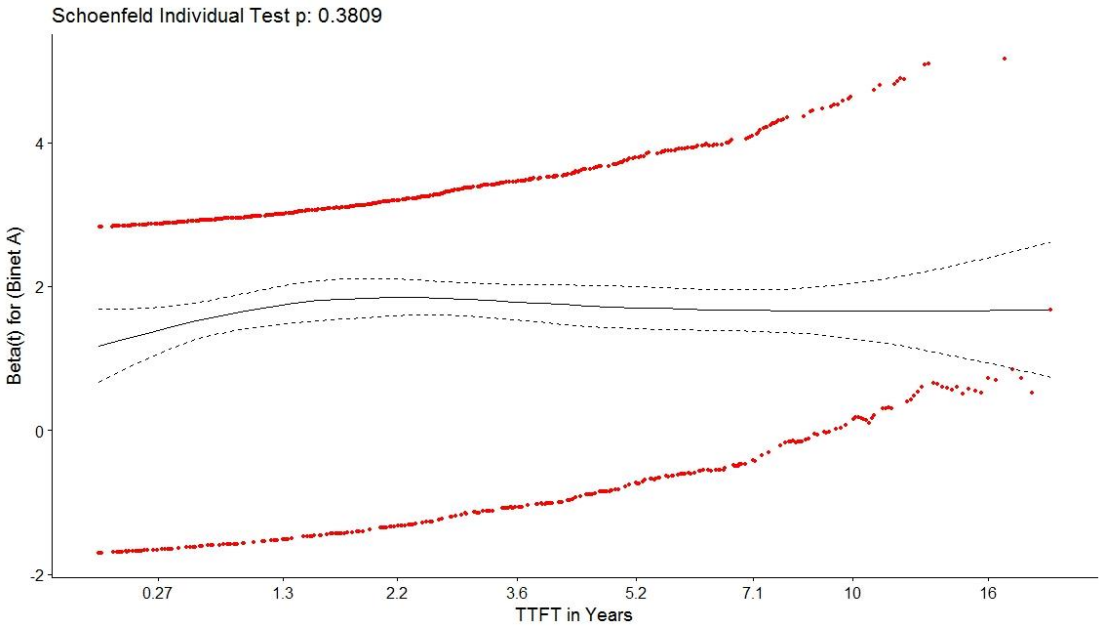

NOTCH1 & Binet A
Hazard difference: U−M
Hazard ratio: U/M
Hazard difference: U−M*
Hazard ratio: U/M*
Hazard difference
Hazard ratio
TTFT in years
0.05
0.10
0.15
0.20
0.25
0.30
0.35
2
4
6
8
0
2
4
6
8
10

**S8F**

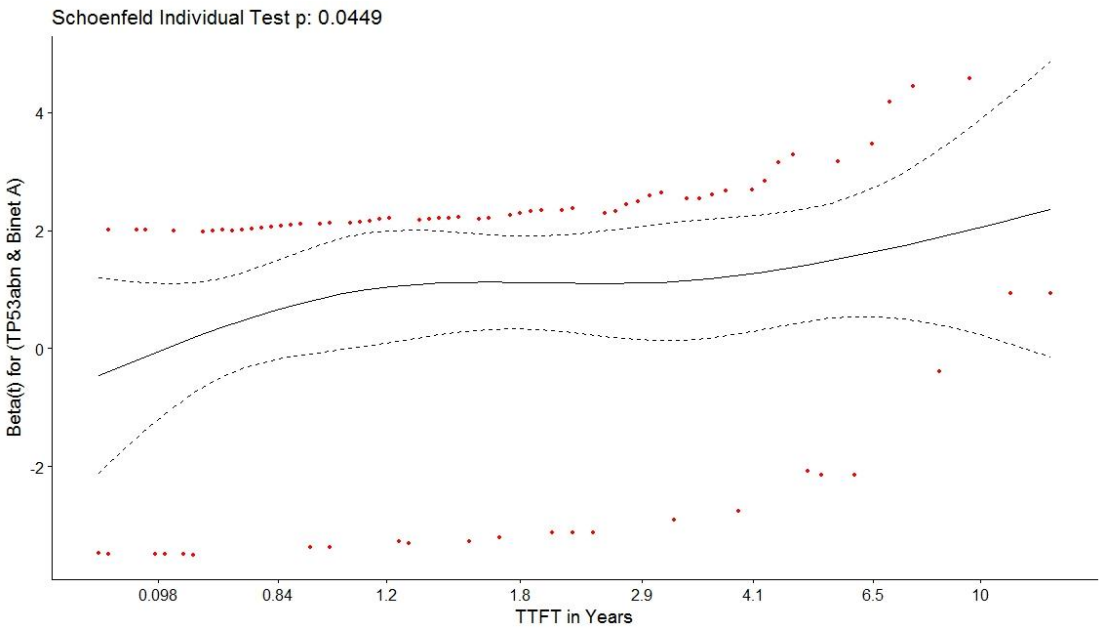

SF3B1 & Binet A
Hazard difference: U−M
Hazard ratio: U/M
Hazard difference: U−M*
Hazard ratio: U/M*
Hazard difference
Hazard ratio
TTFT in years
0.05
0.10
0.15
0.20
0.25
0.30
0.35
2
4
6
8
0
2
4
6
8
10

**Supplemental Figure 9:** The Schoefeld residuals are displayed for all the subgroups considered. In particular, S9A corresponds to the entire cohort, S9B to patients with *TP53* aberrations [*TP53*abn, del(17p) and/or *TP53* mutations], S9C to del(11q), non *TP53*abn cases, S9D to cases carrying trisomy 12 with no *TP53*abn, S9E to del(13q)/normal FISH cases, S9F to *NOTCH1* mutations, and S9G to *SF3B1* mutations. The p-value referring to the evaluation of the proportional hazards assumption, based on the Schoefeld residuals is also displayed. The assumption of proportional hazards between M-CLL and U-CLL was rejected only for the *TP53*abn patients.

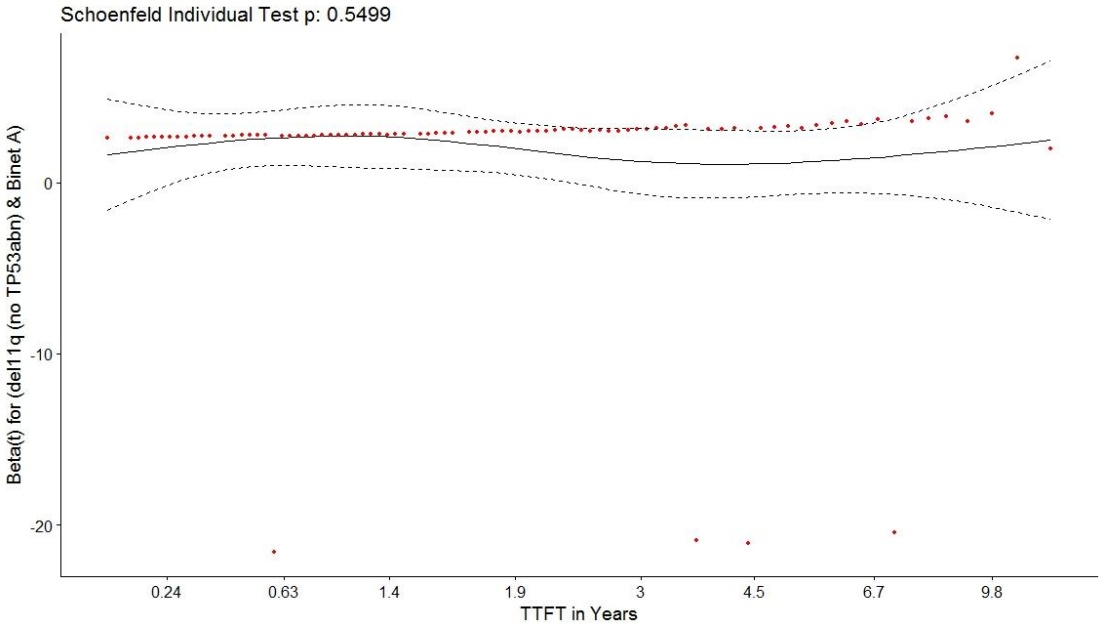
**S9A**



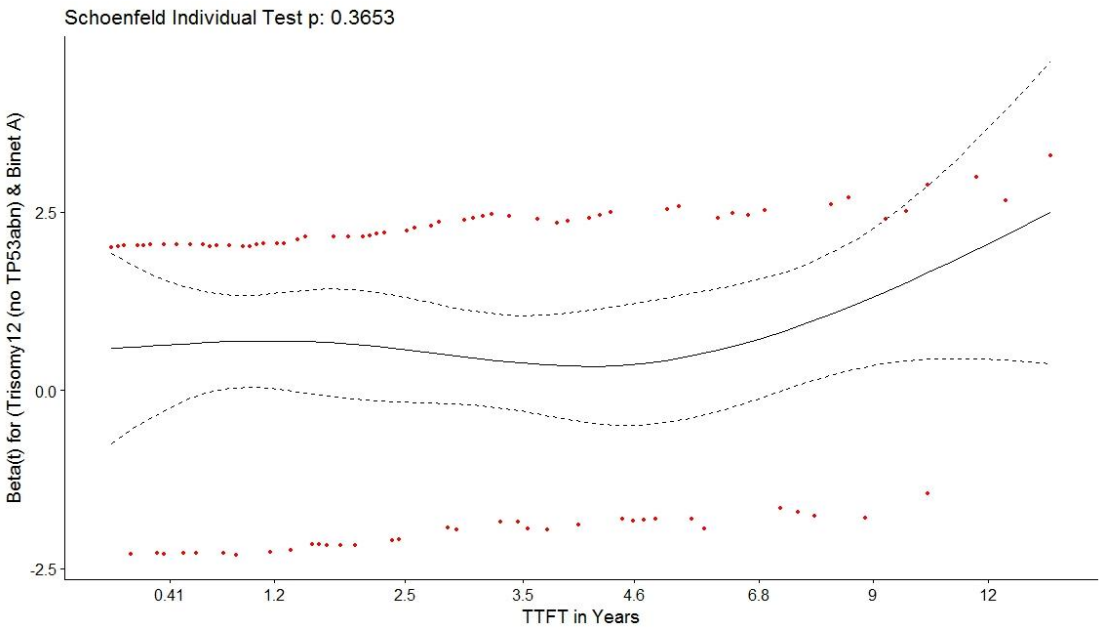
**S9B**


Schoenfeld Individual Test p: 0.0449
Beta(t) for (TP53abn & Binet A)
4
2
0
-2
0.098
0.84
1.2
1.8
2.9
4.1
6.5
10
TTFT in Years

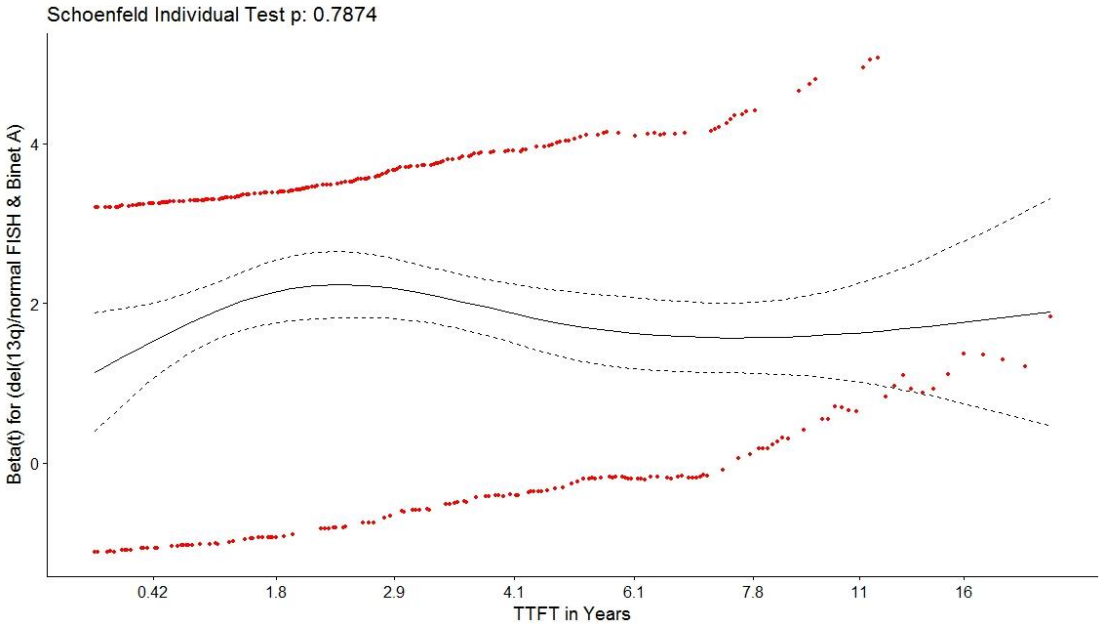
**S9C**


Schoenfeld Individual Test p: 0.5499
Beta(t) for (del11q (no TP53abn) & Binet A)
0
-10
-20
0.24
0.63
1.4
1.9
3
4.5
6.7
9.8
TTFT in Years

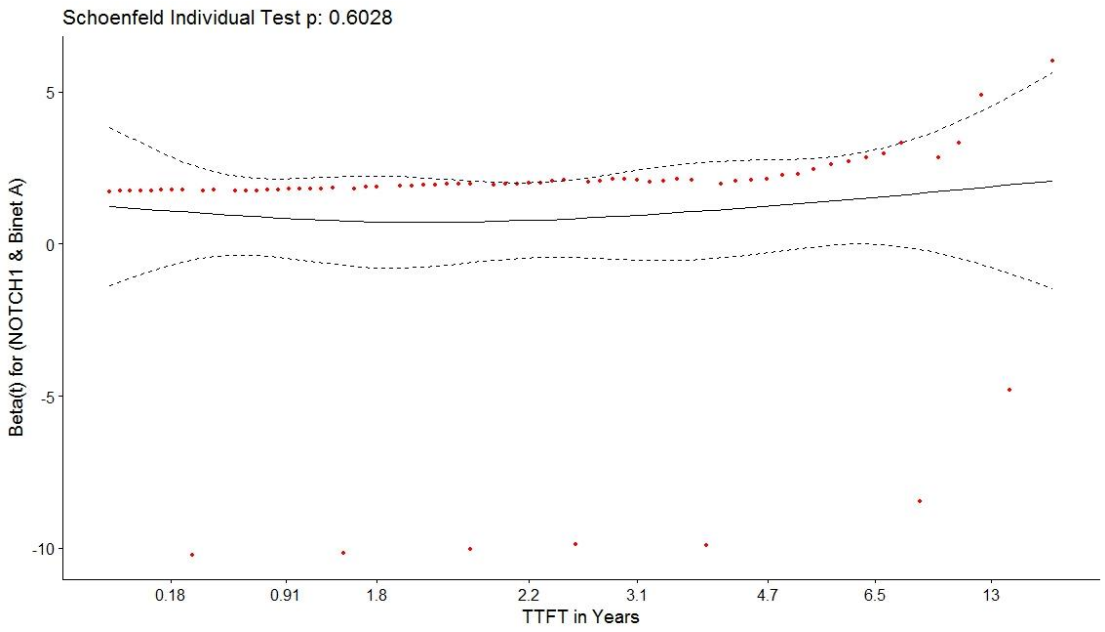
**S9D**


Schoenfeld Individual Test p: 0.3653
Beta(t) for (Trisomy12 (no TP53abn) & Binet A)
2.5
0.0
-2.5
0.41
1.2
2.5
3.5
4.6
6.8
9
12
TTFT in Years

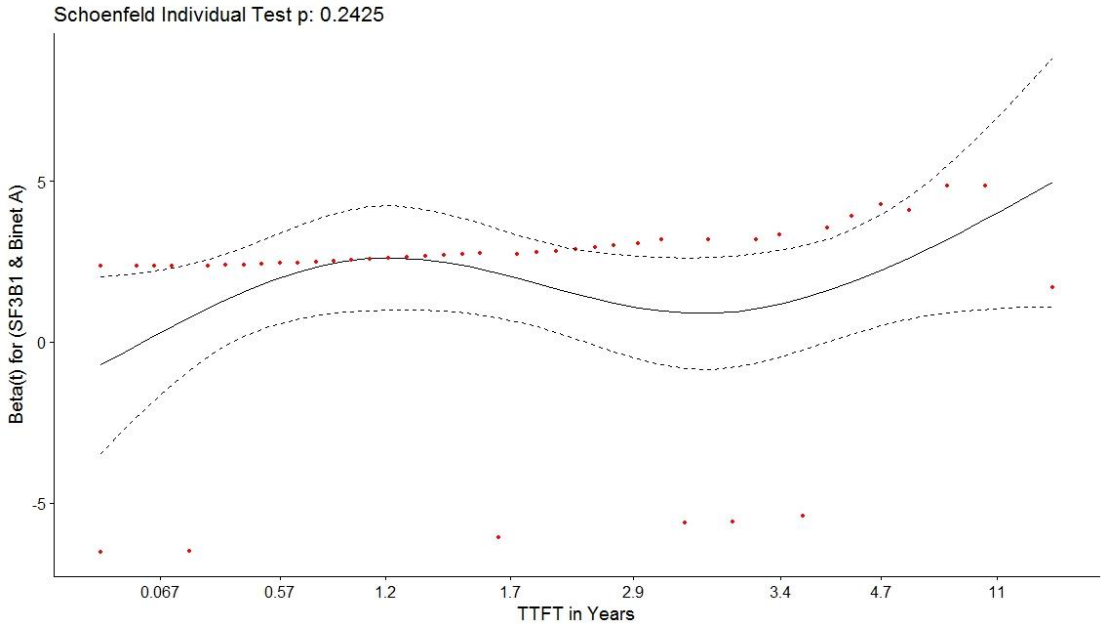
**S9E**


Schoenfeld Individual Test p: 0.7874
Beta(t) for (del(13q)/normal FISH & Binet A)
4
2
0
0.42
1.8
2.9
4.1
6.1
7.8
11
16
TTFT in Years

**S9F**


Schoenfeld Individual Test p: 0.6028
Beta(t) for (NOTCH1 & Binet A)
5
0
-5
-10
0.18
0.91
1.8
2.2
3.1
4.7
6.5
13
TTFT in Years

**S9G**


Schoenfeld Individual Test p: 0.2425
Beta(t) for (SF3B1 & Binet A)
5
0
-5
0.067
0.57
1.2
1.7
2.9
3.4
4.7
11
TTFT in Years