Prognostic and predictive role of gene mutations in chronic lymphocytic leukemia: results from the pivotal phase III study COMPLEMENT1

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Received: June 10, 2019.
Accepted: January 7, 2020.
Pre-published: January 9, 2020.
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**Supp. table 1:**

Clinical and biological characteristics of full trial population of the complement 1 trial (n=447) and of the analysed cohort (n=383).

| Patients          | analysed cohort (n=383) | full trial (n=447) |
|-------------------|-------------------------|--------------------|
| Binet C           | 113 (29.5%)             | 139 (31.1%)        |
| Male              | 246 (64.2%)             | 282 (63.1%)        |
| B-Symptoms        | 214 (55.9%)             | 240 (53.7%)        |
| IGHV              | 199 (52%)               | 226 (50.6%)        |
| B2MG >5mg/l       | 168 (43.9%)             | 196 (43.8%)        |
| del11q            | 58 (15.1%)              | 64 (14.3%)         |
| del17p            | 19 (5%)                 | 26 (5.8%)          |
| Chl+O             | 183 (47.8%)             | 217 (48.5%)        |
| ECOG>=1           | 142 (37.1%)             | 170 (38%)          |
| Age =>75          | 96 (25.1%)              | 119 (26.6%)        |
| CIRS>=8           | 236 (61.6%)             | 275 (61.5%)        |
| WBC >50           | 226 (59%)               | 257 (57.5%)        |
| CR rate           | 28 (7.3%)               | 30 (6.7%)          |
| ORR               | 296 (77.3%)             | 336 (75.2%)        |
| mPFS Clb (months) | 12.8                    | 13.1               |
| mPFS O-Clb (months) | 22.4              | 22.6               |
Supp. table 2:

Details of gene mutations identified in Complement1 including position dDNA and protein position, mutation type and variant frequency (VF).

| SampleID | Gene     | Genomic description (hg19) | Protein description | type       | VF  |
|----------|----------|----------------------------|---------------------|------------|-----|
| 75644638 | ATM      | g.chr11:108098352A>T      | p.M1L               | missense   | 0.09+|
| 75624287 | ATM      | g.chr11:108099973C>G      | p.S85*              | nonsense   | 0.08+|
| 75623093 | ATM      | g.chr11:108115600C>T      | p.R250*             | nonsense   | 0.48+|
| 75622919 | ATM      | g.chr11:108117784A>G      | p.Y332C             | missense   | 0.80+|
| 75624010 | ATM      | g.chr11:108121532G>A      | p.R447Q             | missense   | 0.57+|
| 75624191 | ATM      | g.chr11:108129749C>T      | p.R805*             | nonsense   | 0.50+|
| 75642552 | ATM      | g.chr11:108137953A>C      | p.D841A             | missense   | 0.50+|
| 75624035 | ATM      | g.chr11:108138012T>A      | p.Y861N             | missense   | 0.50+|
| 75623126 | ATM      | g.chr11:1081418474G>T     | p.? splice site     | missense   | 0.35+|
| 99293053 | ATM      | g.chr11:108141988T>C      | p.S978P             | missense   | 0.45+|
| 99294189 | ATM      | g.chr11:108143448G>A      | p.? splice site     | missense   | 0.15+|
| 99294528 | ATM      | g.chr11:108143467C>T      | p.W1058R            | missense   | 0.86+|
| 75645142 | ATM      | g.chr11:108143540A>G      | p.H1082R            | missense   | 0.64+|
| 75642181 | ATM      | g.chr11:108151768G>C      | p.R1150T            | missense   | 0.49+|
| 75622394 | ATM      | g.chr11:108155132G>A      | p.A1309T            | missense   | 0.89+|
| 99292938 | ATM      | g.chr11:108155132G>A      | p.A1309T            | missense   | 0.49+|
| 75623077 | ATM      | g.chr11:108155132G>A      | p.? splice site     | missense   | 0.74+|
| 99294308 | ATM      | g.chr11:108170477T>C      | p.I1681T            | missense   | 0.51+|
| 75623471 | ATM      | g.chr11:108170479G>T      | p.D1682Y            | missense   | 0.15+|
| 99294562 | ATM      | g.chr11:108170576T>A      | p.M1714K            | missense   | 0.61+|
| 75623218 | ATM      | g.chr11:108170588T>A      | p.L1718Q            | missense   | 0.11+|
| 75622916 | ATM      | g.chr11:108173578A>G      | p.? splice site     | missense   | 0.74+|
| 99295497 | ATM      | g.chr11:108175528C>T      | p.R1875*            | nonsense   | 0.08+|
| 75642992 | ATM      | g.chr11:108178641C>T      | p.R1898*            | nonsense   | 0.36+|
| 75623077 | ATM      | g.chr11:108183221T>A      | p.L2001*            | nonsense   | 0.92+|
| 75622394 | ATM      | g.chr11:108186598T>C      | p.Y2019H            | missense   | 0.64+|
| 75622837 | ATM      | g.chr11:108186740T>C      | p.L2033P            | missense   | 0.81+|
| 75621166 | ATM      | g.chr11:108189756C>A      | p.T2035K            | missense   | 0.86+|
| 99294655 | ATM      | g.chr11:108189757G>A      | p.E2039K            | missense   | 0.44+|
| 75622640 | ATM      | g.chr11:108190788A>C      | p.? splice site     | missense   | 0.45+|
| 99295579 | ATM      | g.chr11:108192066A>T      | p.E2164V            | missense   | 0.08+|
| 99294163 | ATM      | g.chr11:108196143C>T      | p.R2227C            | nonsense   | 0.38+|
| 75645227 | ATM      | g.chr11:108196851C>T      | p.Q2292*            | nonsense   | 0.40+|
| 75645303 | ATM      | g.chr11:108198427G>A      | p.W2344*            | nonsense   | 0.55+|
| 75623093 | ATM      | g.chr11:108198454C>T      | p.P2353L            | missense   | 0.43+|
| 75623899 | ATM      | g.chr11:10819837T>G       | p.F2393L            | missense   | 0.08+|
| 75623164 | ATM      | g.chr11:10819853C>T      | p.Q2399*            | nonsense   | 0.50+|
| Position | Gene | Chromosome | Variant | Description | Frequency |
|----------|------|------------|---------|-------------|-----------|
| 75623164 | ATM  | g.chr11:108200976A>T | p.D2448V | missense | 0.14 + |
| 75646539 | ATM  | g.chr11:108201081G>A | p.W2483* | nonsense | 0.07 + |
| 99293079 | ATM  | g.chr11:108201096G>A | p.C2488Y | missense | 0.90 + |
| 99295509 | ATM  | g.chr11:108206578G>A | p.D2720N | missense | 0.80 + |
| 75624191 | ATM  | g.chr11:108206581G>A | p.D2721N | missense | 0.49 + |
| 75624711 | ATM  | g.chr11:108216637T>A | p.? | splice site | 0.19 + |
| 75623214 | ATM  | g.chr11:108218089C>G | p.L2890V | missense | 0.17 + |
| 75623282 | ATM  | g.chr11:108225594T>C | p.I2948T | missense | 0.95 + |
| 75622804 | ATM  | g.chr11:108236086C>T | p.R3008C | missense | 0.96 + |
| 75642131 | ATM  | g.chr11:108236086C>T | p.R3008C | missense | 0.83 + |
| 99294189 | ATM  | g.chr11:108236087G>A | p.R3008H | missense | 0.14 + |
| 75643260 | ATM  | g.chr11:108236087G>A | p.R3008H | missense | 0.14 + |
| 75623078 | ATM  | g.chr11:108236096T>A | p.M3011K | missense | 0.08 + |
| 99295520 | ATM  | g.chr11:108236213C>T | p.P3050L | missense | 0.51 + |
| 75623212 | BIRC3 | g.chr11:102201909_102201909del1 | p.F421fs | frame_shift_del | 0.53 + |
| 75622919 | BIRC3 | g.chr11:102201945G>T | p.E433* | nonsense | 0.71 + |
| 75623222 | BIRC3 | g.chr11:102201970C>G | p.S441* | nonsense | 0.13 + |
| 75623329 | BIRC3 | g.chr11:1022019964C>G | p.? | splice site | 0.44 + |
| 75623997 | BIRC3 | g.chr11:102206924G>A | p.E518K | missense | 0.41 + |
| 75623222 | BIRC3 | g.chr11:102207512T>G | p.I534S | missense | 0.07 + |
| 75623222 | BIRC3 | g.chr11:102207518C>T | p.T536R | missense | 0.14 + |
| 75623222 | BIRC3 | g.chr11:102207523G>T | p.D538Y | missense | 0.14 + |
| 99295329 | BIRC3 | g.chr11:102207651G>T | p.E545* | nonsense | 0.43 + |
| 99295580 | BIRC3 | g.chr11:102207656_102207657del1 | p.D546fs | frame_shift_del | 0.44 + |
| 75642984 | BIRC3 | g.chr11:102207697G>A | p.C560Y | missense | 0.68 + |
| 99294283 | BIRC3 | g.chr11:102207756G>T | p.D580Y | missense | 0.54 + |
| 75642575 | FBXW7 | g.chr4:153244303T>C | p.? | splice site | 0.45 + |
| 99294628 | FBXW7 | g.chr4:153247171A>G | p.V544A | missense | 0.20 + |
| 75622951 | FBXW7 | g.chr4:153247294G>A | p.A503V | missense | 0.47 + |
| 99295316 | FBXW7 | g.chr4:153247366C>T | p.R479Q | missense | 0.10 + |
| 99294721 | FBXW7 | g.chr4:153247366C>T | p.R479Q | missense | 0.39 + |
| 75622630 | FBXW7 | g.chr4:153249384C>T | p.R465H | missense | 0.32 + |
| 75623209 | FBXW7 | g.chr4:153249385G>A | p.R465C | missense | 0.32 + |
| 99295202 | FBXW7 | g.chr4:153249385G>A | p.R465C | missense | 0.32 + |
| 75646433 | FBXW7 | g.chr4:153249504C>A | p.W425L | missense | 0.35 + |
| 75623502 | FBXW7 | g.chr4:153268222T>C | p.T196A | missense | 0.43 + |
| 75623981 | FBXW7 | g.chr4:153332910_153332911_ins3 | p.G16A | in_frame_ins | 0.46 + |
| 75623579 | FBXW7 | g.chr4:153244092G>A | p.R689W | missense | 0.41 + |
| 75642984 | FBXW7 | g.chr4:153244229T>A | p.D643V | missense | 0.47 + |
| 75642984 | FBXW7 | g.chr4:153244268A>C | p.L630* | nonsense | 0.55 + |
| 99294139 | MYD88 | g.chr3:38182025G>T | p.V217F | missense | 0.32 + |
| 75623281 | MYD88 | g.chr3:38182025G>T | p.V217F | missense | 0.44 + |
| 75621191 | MYD88 | g.chr3:38182025G>T | p.V217F | missense | 0.34 + |
99295172 MYD88 g.chr3:38182025G>T p.V217F missense 0.26
75623203 MYD88 g.chr3:38182032C>G p.S219C missense 0.20
99294344 MYD88 g.chr3:38182032C>G p.S219C missense 0.32
99293452 MYD88 g.chr3:38182032C>G p.S219C missense 0.26
75622905 MYD88 g.chr3:38182641T>C p.L265P missense 0.16
75622516 MYD88 g.chr3:38182641T>C p.L265P missense 0.42
75622670 MYD88 g.chr3:38182641T>C p.L265P missense 0.40
75646539 NOTCH1 g.chr9:139,390,145T>C p.? 3'UTR -
99294652 NOTCH1 g.chr9:139,390,145T>C p.? 3'UTR -
75623165 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
99295184 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
75624112 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
75623454 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
75622399 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
99293071 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
75622956 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
75623471 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
99295452 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
99295329 NOTCH1 g.chr9:139,390,152T>C p.? 3'UTR -
99295163 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.12 +
75622435 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.1 +
75622440 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.09 +
75623050 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.24 +
75623126 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.25 +
75623230 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.47 +
75624585 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.2 +
99294423 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.47 +
75622317 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.53 +
75622346 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.32 +
75623188 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.47 +
75623189 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.48 +
75623997 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.19 +
75623998 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.49 +
99293603 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.2 +
99294365 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.48 +
75622829 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.26 +
75622916 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.06 +
99293238 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.31 +
99294447 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.31 +
99295329 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.07 +
99295664 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.49 +
75622598 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.42 +
75622863 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.77 +
75623236 NOTCH1 g.chr9:139390649_139390650del2 p.P2514fs frame_shift_del 0.44 +
| Gene      | Chromosome | Position       | Variant          | Mutation                  | Frequency | Effect  |
|-----------|------------|----------------|------------------|---------------------------|-----------|---------|
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.27      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.06      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.14      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.64      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.58      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.3       |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.4       |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.16      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.43      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.06      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.43      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.37      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.37      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.4       |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.43      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.07      |         |
| NOTCH1    | chr9:139390649-139390650del2 | g.chr9:139390649_139390650del2 | p.P2514fs         | frame_shift_del           | 0.41      |         |
| POT1      | chr7:124475458-124475460del2 | g.chr7:124481141A>T | p.Y2444*         | nonsense                  | 0.45      |         |
| POT1      | chr7:124482894G>A | g.chr7:124482894G>A | p.Q2441*         | nonsense                  | 0.54      |         |
| POT1      | chr7:124482937G>A | g.chr7:124482937G>A | p.Q2409*         | nonsense                  | 0.31      |         |
| POT1      | chr7:124493075C>T | g.chr7:124493075C>T | p.G274R          | missense                  | 0.35      |         |
| POT1      | chr7:124493077C>T | g.chr7:124493077C>T | p.R273Q          | missense                  | 0.22      |         |
| POT1      | chr7:124493098T>G | g.chr7:124493098T>G | p.H266P          | missense                  | 0.41      |         |
| POT1      | chr7:124493142G>A | g.chr7:124493142G>A | p.A2250V         | missense                  | 0.59      |         |
| POT1      | chr7:124493170T>C | g.chr7:124493170T>C | p.M251I          | missense                  | 0.49      |         |
| POT1      | chr7:124493176C>T | g.chr7:124493176C>T | p.S243I          | missense                  | 0.34      |         |
| ID          | Gene | Chromosome | Position | Codon Change | Type         | Probability |
|-------------|------|------------|----------|--------------|--------------|-------------|
| 99294652    | POT1 | g.chr7:124499043 | C>T      | p.D224N      | missense     | 0.47        |
| 99293060    | POT1 | g.chr7:124503519 | A>G      | p.M144T      | missense     | 0.48        |
| 99295531    | POT1 | g.chr7:124503636 | G>A      | p.T105M      | missense     | 0.46        |
| 75623400    | POT1 | g.chr7:124503682 | C>T      | p.K90E       | missense     | 0.46        |
| 99292358    | POT1 | g.chr7:124503687 | A>G      | p.V88A       | missense     | 0.49        |
| 99293371    | POT1 | g.chr7:124510963 | G>A      | p.?          | splice site  | 0.14        |
| 99293416    | POT1 | g.chr7:124510966 | T>C      | p.K85R       | missense     | 0.49        |
| 75646555    | POT1 | g.chr7:124510987 | G>A      | p.I78T       | missense     | 0.48        |
| 99295184    | POT1 | g.chr7:124511014 | A>G      | p.M144T      | missense     | 0.40        |
| 75624035    | POT1 | g.chr7:124511080 | A>T      | p.V47E       | missense     | 0.31        |
| 75645174    | POT1 | g.chr7:124510963 | ?        | p.?          | splice site  | 0.34        |
| 99293038    | POT1 | g.chr7:124532329 | T>C      | p.K85R       | missense     | 0.46        |
| 75622429    | POT1 | g.chr7:124532330 | T>C      | p.K85R       | missense     | 0.32        |
| 99293238    | POT1 | g.chr7:124532393 | A>G      | p.I78T       | missense     | 0.38        |
| 75623997    | POT1 | g.chr7:124532398 | A>G      | p.Q16*       | nonsense     | 0.10        |
| 75622435    | POT1 | g.chr7:124537227 | T>C      | p.M1V        | missense     | 0.33        |
| 75623998    | POT1 | g.chr7:124537227 | T>C      | p.M1V        | missense     | 0.49        |
| 75622611    | POT1 | g.chr7:124537267 | A>G      | p.?          | splice site  | 0.38        |
| 0075622402  | RPS15| g.chr19:1440414 | T>C      | p.L69R       | missense     | -           |
| 0075642392  | RPS15| g.chr19:1440414 | T>C      | p.L69R       | missense     | -           |
| 0075623579  | RPS15| g.chr19:1440415 | T>C      | p.L69R       | missense     | -           |
| 0075623228  | RPS15| g.chr19:1440417 | T>C      | p.L69R       | missense     | -           |
| 0075622390  | RPS15| g.chr19:1440424 | G>A      | p.A135G      | missense     | -           |
| 0075622647  | RPS15| g.chr19:1440429 | A>G      | p.T136A      | missense     | -           |
| 0099294365  | RPS15| g.chr19:1440432 | T>C      | p.H137Y      | missense     | -           |
| 0075623997  | RPS15| g.chr19:1440432 | T>C      | p.H137Y      | missense     | -           |
| 0099294308  | RPS15| g.chr19:1440436 | T>C      | p.S138F      | missense     | -           |
| 0099293452  | RPS15| g.chr19:1440436 | T>C      | p.S138F      | missense     | -           |
| 0075623165  | RPS15| g.chr19:1440436 | T>C      | p.S138F      | missense     | -           |
| 0099294271  | RPS15| g.chr19:1440439 | T>C      | p.S139F      | missense     | -           |
| 0099293370  | RPS15| g.chr19:1440439 | T>C      | p.S139F      | missense     | -           |
| 0075645275  | RPS15| g.chr19:1440456 | A>G      | p.K145Q      | missense     | -           |
| 0020203710  | RPS15| g.chr19:1440457 | T>C      | p.?          | nonsense     | -           |
| 0075623223  | RPS15| g.chr19:1440458 | G>A      | p.K145N      | missense     | -           |
| 99293347    | SF3B1| g.chr2:198265474 | G>A      | p.G895R      | missense     | 0.33        |
| 75645830    | SF3B1| g.chr2:198265593 | T>C      | p.D855G      | missense     | 0.32        |
| 75623185    | SF3B1| g.chr2:198266488 | T>C      | p.E783G      | missense     | 0.4         |
| 75623267    | SF3B1| g.chr2:198266512 | T>C      | p.R775Q      | missense     | 0.12        |
| 75624045    | SF3B1| g.chr2:198266512 | T>C      | p.R775Q      | missense     | 0.26        |
| 75643260    | SF3B1| g.chr2:198266611 | T>C      | p.G742D      | missense     | 0.1         |
| 75622310    | SF3B1| g.chr2:198266611 | T>C      | p.G742D      | missense     | 0.14        |
| 99293452    | SF3B1| g.chr2:198266611 | T>C      | p.G742D      | missense     | 0.16        |
| 75623981    | SF3B1| g.chr2:198266611 | T>C      | p.G742D      | missense     | 0.18        |
| Sample ID | Genomic Location | Allele | Protein Effect | Frequency |
|-----------|------------------|--------|----------------|-----------|
| 99295452  | SF3B1 g.chr2:198266611C>T | p.G742D missense | 0.26 |
| 75624222  | SF3B1 g.chr2:198266611C>T | p.G742D missense | 0.3 |
| 99293108  | SF3B1 g.chr2:198266611C>T | p.G742D missense | 0.36 |
| 99292900  | SF3B1 g.chr2:198266611C>T | p.G742D missense | 0.41 |
| 75622635  | SF3B1 g.chr2:198266611C>T | p.G742D missense | 0.43 |
| 99295800  | SF3B1 g.chr2:198266611C>T | p.G742D missense | 0.45 |
| 75623078  | SF3B1 g.chr2:198266709C>A | p.K741N missense | 0.08 |
| 75624616  | SF3B1 g.chr2:198266713C>T | p.G740E missense | 0.08 |
| 75624045  | SF3B1 g.chr2:198266821A>T | p.I704N missense | 0.16 |
| 99293370  | SF3B1 g.chr2:198266822T>A | p.I704F missense | 0.29 |
| 99294344  | SF3B1 g.chr2:198266822T>A | p.I704F missense | 0.38 |
| 99295168  | SF3B1 g.chr2:198266822T>A | p.I704F missense | 0.4 |
| 75624174  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.07 |
| 99294652  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.08 |
| 75624616  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.08 |
| 75645300  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.09 |
| 99294189  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.16 |
| 75622479  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.21 |
| 75644240  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.21 |
| 75644614  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.41 |
| 75623833  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.41 |
| 75623400  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.42 |
| 75623661  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.43 |
| 99293084  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.43 |
| 75623297  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.46 |
| 75646555  | SF3B1 g.chr2:198266834T>C | p.K700E missense | 0.47 |
| 75624222  | SF3B1 g.chr2:198267359C>G | p.K666N missense | 0.08 |
| 75623584  | SF3B1 g.chr2:198267359C>G | p.K666N missense | 0.18 |
| 99294163  | SF3B1 g.chr2:198267360T>G | p.K666T missense | 0.31 |
| 99295436  | SF3B1 g.chr2:198267360T>G | p.K666T missense | 0.43 |
| 99294563  | SF3B1 g.chr2:198267360T>G | p.K666T missense | 0.43 |
| 75623232  | SF3B1 g.chr2:198267361T>C | p.K666E missense | 0.43 |
| 99295079  | SF3B1 g.chr2:198267369G>A | p.T663I missense | 0.37 |
| 75622733  | SF3B1 g.chr2:198267369G>A | p.T663I missense | 0.35 |
| 75622414  | SF3B1 g.chr2:198267373G>C | p.H662D missense | 0.46 |
| 75645142  | SF3B1 g.chr2:198267373G>C | p.H662D missense | 0.39 |
| 99293079  | SF3B1 g.chr2:198267480T>C | p.N626S missense | 0.14 |
| 75642131  | SF3B1 g.chr2:198267480T>C | p.N626S missense | 0.25 |
| 75624272  | SF3B1 g.chr2:198267481T>A | p.N626Y missense | 0.45 |
| 99294338  | SF3B1 g.chr2:198267483C>A | p.R625L missense | 0.28 |
| 75645828  | SF3B1 g.chr2:198267483C>T | p.R625H missense | 0.44 |
| 75623308  | SF3B1 g.chr2:198267489T>C | p.Y623C missense | 0.16 |
| 99293540  | SF3B1 g.chr2:198267489T>C | p.Y623C missense | 0.12 |
| 75624601  | SF3B1 g.chr2:198267489T>C | p.Y623C missense | 0.4 |
| Gene       | Chromosome  | HGVS | Mutation Type | p.Amino Acid Change | Probability |
|------------|-------------|------|---------------|---------------------|-------------|
| SF3B1      | chr2        | g.chr2:198267489T>C | missense | p.Y623C             | 0.17        |
| SF3B1      | chr2        | g.chr2:198267491C>A | missense | p.E622D             | 0.47        |
| SF3B1      | chr2        | g.chr2:198267498A>T | missense | p.M620K             | 0.33        |
| SF3B1      | chr2        | g.chr2:198267510T>A | missense | p.D616V             | 0.44        |
| SF3B1      | chr2        | g.chr2:198267512T>A | missense | p.D618E             | 0.38        |
| TP53       | chr17       | g.chr17:7572958A>T | missense | p.M384T             | 0.54        |
| TP53       | chr17       | g.chr17:7572989C>G | missense | p.G374R             | 0.47        |
| TP53       | chr17       | g.chr17:7576919_7576919del1 | frame_shift_del | p.R280Q              | 0.44        |
| TP53       | chr17       | g.chr17:7577093_7577094ins8 | frame_shift_del | p.R282fs             | 0.87        |
| TP53       | chr17       | g.chr17:7577091G>A | missense | p.R282Q              | 0.82        |
| TP53       | chr17       | g.chr17:7577095G>C | missense | p.D281E              | 0.41        |
| TP53       | chr17       | g.chr17:7577096T>C | missense | p.D281G              | 0.44        |
| TP53       | chr17       | g.chr17:7577097T>C | missense | p.D281G              | 0.60        |
| TP53       | chr17       | g.chr17:7577100T>C | missense | p.R280G              | 0.28        |
| TP53       | chr17       | g.chr17:7577111G>T | missense | p.A276D              | 0.45        |
| TP53       | chr17       | g.chr17:7577124C>T | missense | p.V272M              | 0.45        |
| TP53       | chr17       | g.chr17:7577498C>T | splice site | p.?                   | 0.77        |
| TP53       | chr17       | g.chr17:7577506C>A | missense | p.D259Y              | 0.84        |
| TP53       | chr17       | g.chr17:7577539G>A | missense | p.R248W              | 0.44        |
| TP53       | chr17       | g.chr17:7578190T>C | missense | p.R248W              | 0.44        |
| TP53       | chr17       | g.chr17:7578244C>G | missense | p.R202P              | 0.51        |
| TP53       | chr17       | g.chr17:7578262G>C | missense | p.R196P              | 0.43        |
| TP53       | chr17       | g.chr17:7578263G>A | nonsense | p.R196*              | 0.42        |
| TP53       | chr17       | g.chr17:7578394T>C | missense | p.H179R              | 0.20        |
| TP53       | chr17       | g.chr17:7578394T>C | missense | p.H179R              | 0.39        |
| TP53       | chr17       | g.chr17:7578394T>C | missense | p.H179R              | 0.32        |
| TP53       | chr17       | g.chr17:7578490A>T | missense | p.H179Y              | 0.79        |
| TP53       | chr17       | g.chr17:7578457C>T | missense | p.R158H              | 0.28        |
| TP53       | chr17       | g.chr17:7578490A>T | missense | p.R147D              | 0.61        |
| TP53       | chr17       | g.chr17:7578490A>T | missense | p.W147fs             | 0.05        |
| TP53       | chr17       | g.chr17:7578517G>A | missense | p.A138V              | 0.86        |
| TP53       | chr17       | g.chr17:7578535T>C | missense | p.K132R              | 0.82        |
| TP53       | chr17       | g.chr17:7579350A>C | missense | p.F113V              | 0.79        |
| TP53       | chr17       | g.chr17:7579377G>A | nonsense | p.Q104*              | 0.74        |
| TP53       | chr17       | g.chr17:7579528C>T | nonsense | p.W53*               | 0.89        |
| TP53       | chr17       | g.chr17:7577538C>T | missense | p.R248Q              | 0.86        |
| TP53       | chr17       | g.chr17:7577106A>T | missense | p.R278S              | 0.96        |
| TP53       | chr17       | g.chr17:7577550C>T | missense | p.G244D              | 0.39        |
| TP53       | chr17       | g.chr17:7577120C>T | missense | p.R273H              | 0.18        |
| Variant ID | Gene | Chromosome:Position | Variant Type | Mutation Type | p-value |
|------------|------|---------------------|--------------|---------------|---------|
| 75641558   | TP53 | chr17:7577120C>A    |              | p.R273L      | 0.84    |
| 75622402   | TP53 | chr17:7578406C>T    |              | p.R175H      | 0.29    |
| 99293540   | TP53 | chr17:7578479G>A    |              | p.P151S      | 0.16    |
Supp. table 3:

Associations of clinical, laboratory and genetic parameters with gene mutations. Incidences, odds ratio and p value is given for presence vs. absence of each parameter.

| Parameter                  | TP53 Incidence | TP53 Odds ratio | TP53 p | SF3B1 Incidence | SF3B1 Incidence | SF3B1 Odds ratio | SF3B1 p | NOTCH1 Incidence | NOTCH1 Incidence | NOTCH1 Odds ratio | NOTCH1 p | ATM Incidence | ATM Odds ratio | ATM p | RPS15 Incidence | RPS15 Odds ratio | RPS15 p |
|----------------------------|----------------|-----------------|--------|-----------------|-----------------|------------------|--------|-----------------|-----------------|------------------|--------|---------------|----------------|-------|----------------|----------------|--------|
| Male sex                   | 9% vs. 12%     | 0.78            | 0.48   | 17% vs. 9%      | 2.14            | 0.03             |        | 17% vs. 28%     | 0.59            | 0.06             |        | 16% vs. 9%    | 1.83            | 0.1   | 5% vs. 4%      | 1.83            | 0.1   |
| Age >70y                   | 13% vs. 8%     | 1.86            | 0.09   | 13% vs. 16%     | 0.78            | 0.46             |        | 18% vs. 22%     | 0.82            | 0.55             |        | 12% vs. 14%   | 0.86            | 0.75  | 3% vs. 6%      | 0.44            | 0.14  |
| Binet C                    | 14% vs. 9%     | 1.77            | 0.1    | 17% vs. 13%     | 1.36            | 0.34             |        | 24% vs. 18%     | 1.29            | 0.41             |        | 11% vs. 14%   | 0.75            | 0.49  | 6% vs. 4%      | 1.32            | 0.59  |
| Splenomegaly               | 9% vs. 6%      | 1.55            | 0.4    | 16% vs. 13%     | 1.27            | 0.51             |        | 24% vs. 17%     | 1.46            | 0.28             |        | 15% vs. 11%   | 1.47            | 0.37  | 5% vs. 3%      | 1.61            | 0.57  |
| Bone marrow infiltrate     | 10% vs. 10%    | 0.98            | 1      | 14% vs. 14%     | 1.04            | 1                |        | 0% vs. 21%      | -               | -                |        | 11% vs. 21%   | 0.54            | 0.09  | 5% vs. 4%      | 1.39            | 0.77  |
| B-symptoms                 | 9% vs. 11%     | 0.81            | 0.61   | 16% vs. 11%     | 1.54            | 0.18             |        | 20% vs. 22%     | 0.91            | 0.78             |        | 15% vs. 11%   | 1.34            | 0.43  | 4% vs. 5%      | 0.88            | 0.81  |
| high b2MG                  | 14% vs. 6%     | 2.49            | 0.01   | 17% vs. 12%     | 1.46            | 0.23             |        | 11% vs. 30%     | 0.38            | <0.01           |        | 15% vs. 12%   | 1.21            | 0.63  | 5% vs. 5%      | 0.9             | 1     |
| WBC >50G/L                 | 11% vs. 5%     | 2.59            | 0.05   | 16% vs. 10%     | 1.72            | 0.15             |        | 24% vs. 14%     | 1.74            | 0.08             |        | 18% vs. 8%    | 2.21            | 0.03  | 7% vs. 0%      | -              | <0.01 |
| CIRS≥8                     | 10% vs. 10%    | 1               | 1      | 14% vs. 14%     | 1.07            | 0.88             |        | 22% vs. 18%     | 1.27            | 0.48             |        | 13% vs. 13%   | 1.03            | 1     | 5% vs. 4%      | 1.15            | 1     |
| IGHV unmutated             | 13% vs. 6%     | 2.17            | 0.05   | 16% vs. 12%     | 1.39            | 0.36             |        | 23% vs. 12%     | 2.01            | 0.13             |        | 18% vs. 9%    | 1.95            | 0.07  | 8.5% vs. 0%    | -              | p<0.01|
| del11q                     | 3% vs. 11%     | 0.28            | 0.09   | 19% vs. 13%     | 1.51            | 0.31             |        | 19% vs. 25%     | 0.77            | 0.75             |        | 53% vs. 8%    | 6.58            | <0.01 | 5% vs. 5%      | 1.16            | 0.74  |
| del13q                     | 12% vs. 7%     | 1.81            | 0.12   | 12% vs. 17%     | 0.7             | 0.24             |        | 15% vs. 30%     | 0.48            | 0.01             |        | 14% vs. 13%   | 1.09            | 0.87  | 6% vs. 4%      | 1.78            | 0.32  |
| del17p                     | 89% vs. 6%     | 136             | <0.01  | 0% vs. 15%      | -               | 0.09             |        | 6% vs. 22%      | 0.25            | 0.22             |        | 0% vs. 14%    | -              | 0.15  | 12% vs. 4%     | 2.64            | 0.21  |
| +12q                       | 2% vs. 11%     | 0.14            | 0.03   | 5% vs. 16%      | 0.31            | 0.06             |        | 41% vs. 18%     | 2.24            | 0.02             |        | 8% vs. 14%    | 0.54            | 0.37  | 5% vs. 2%      | 2.86            | 0.49  |
| del6q                      | 25% vs. 10%    | 3.05            | 0.34   | 0% vs. 14       | -               | -                |        | 0% vs. 22%      | -               | -                |        | 0% vs. 14%    | -              | -     | 33% vs. 5%     | 7.22            | 0.17  |
| Parameter              | POT1 Incidence | Odds ratio | p  | BIRC3 Incidence | Odds ratio | p  | MYD88 Incidence | Odds ratio | p  | FBXW7 Incidence | Odds ratio | p  |
|------------------------|----------------|------------|----|----------------|------------|----|----------------|------------|----|----------------|------------|----|
| Male                   | 8% vs. 9%      | 0.9        | 0.84 | 3% vs. 2%      | 1.12       | 1  | 3% vs. 2%      | 1.31       | 1  | 4% vs. 3%      | 1.26       | 0.78 |
| Age >70y               | 9% vs. 8%      | 1.19       | 0.7  | 2% vs. 3%      | 0.54       | 0.51 | 2% vs. 3%      | 0.72       | 0.75 | 4% vs. 3%      | 1.29       | 0.78 |
| Binet C                | 9% vs. 8%      | 1.08       | 0.83 | 2% vs. 3%      | 0.68       | 1  | 4% vs. 2%      | 2.45       | 0.17 | 4% vs. 3%      | 1.06       | 1    |
| Splenomegaly           | 8% vs. 7%      | 1.25       | 0.66 | 2% vs. 2%      | 1.06       | 1  | 4% vs. 2%      | 2.89       | 0.2  | 3% vs. 2%      | 2.15       | 0.48 |
| Bone marrow infiltrate | 8% vs. 7%      | 1.14       | 1    | 2% vs. 2%      | 1.03       | 1  | 3% vs. 2%      | 1.18       | 1    | 3% vs. 5%      | 0.65       | 0.5  |
| High b2MG              | 11% vs. 7%     | 1.58       | 0.25 | 3% vs. 2%      | 1.56       | 0.52 | 2% vs. 2%      | 0.99       | 1    | 4% vs. 3%      | 1.46       | 0.58 |
| WBC >50G/L             | 9% vs. 8%      | 1.05       | 1    | 3% vs. 1%      | 4.14       | 0.27 | 1% vs. 4%      | 0.23       | 0.11 | 4% vs. 2%      | 1.77       | 0.55 |
| CIRS528                | 9% vs. 7%      | 1.42       | 0.43 | 3% vs. 1%      | 2.21       | 0.49 | 2% vs. 4%      | 0.41       | 0.19 | 4% vs. 2%      | 2.12       | 0.39 |
| IGHV unmutated         | 11% vs. 6%     | 1.72       | 0.24 | 5% vs. 0%      | -          | 0.01 | 1% vs. 4%      | 0.11       | 0.02 | 4% vs. 4%      | 0.91       | 1    |
| del11q                 | 5% vs. 9%      | 0.63       | 0.59 | 12% vs. 1%     | 11.79      | <0.01 | 2% vs. 3%      | 0.67       | 1    | 2% vs. 4%      | 0.44       | 0.7  |
| del13q                 | 7% vs. 10%     | 0.75       | 0.56 | 2% vs. 3%      | 0.65       | 0.74 | 3% vs. 1%      | 2.94       | 0.19 | 2% vs. 5%      | 0.35       | 0.09 |
| del17p                 | 0% vs. 9%      | -          | 0.38 | 6% vs. 2%      | 2.39       | 0.38 | 0% vs. 3%      | -          | 1    | 16% vs. 3%     | 6.36       | 0.02 |
| +12q                   | 4% vs. 9%      | 0.41       | 0.28 | 8% vs. 2%      | 4.86       | 0.03 | 2% vs. 3%      | 0.71       | 1    | 11% vs. 2%     | 5.26       | 0.01 |
| del6q                  | 0% vs. 9%      | -          | -    | 0% vs. 3%      | -          | 1    | 0% vs. 2%      | -          | 1    | 0% vs. 0%      | 0          | 1    |
Multivariate analysis for interaction of treatment and biomarker. Therefore the treatment arm, the mutated gene and their interaction were included in the analysis, which was repeated for every gene. Result table shows the hazard ratio (HR), confidence interval (CI 95%) and p-value of the interaction, and therefore the predictive impact.

| Gene     | HR  | CI 95%    | p-value |
|----------|-----|-----------|---------|
| TP53     | 0.77| 0.34-1.74 | 0.53    |
| NOTCH1   | 1.86| 1-3.48    | 0.05    |
| SF3B1    | 1.02| 0.52-1.99 | 0.96    |
| ATM      | 0.89| 0.43-1.83 | 0.75    |
| POT1     | 0.52| 0.21-1.32 | 0.17    |
| RPS15    | 0.94| 0.27-3.33 | 0.92    |
| FBXW7    | 0.93| 0.19-4.55 | 0.92    |
| MYD88    | 0.42| 0.05-3.66 | 0.43    |
| BIRC3    | 0.32| 0.06-1.78 | 0.19    |
Supp. figure 1: Total numbers of patients and mutations subdivided into both treatment arms.
Supp. figure 2:

Associations of gene mutations and chromosomal aberrations considering false discovery rate (FDR). Numbers within the boxes show odd-ratio (lower right number in each box) and p-value categories (upper right number), which can be <0.1, <0.05 or <0.01. Green boxes represent significant co-occurrence (odds ratio >1), red box mutual exclusivity (odds ratio <1). For p-values >0.1, boxes remain bland and numbers are not provided.
Supp. figure 3: Kaplan-Meier estimates of PFS (top panels) and OS (bottom panels) according to the status of gene mutations in POT1, RPS15, FBXW7 and MYD88 for the total patient cohort. Mutated subgroups are depicted by red lines, and wild type by dark blue lines. Denoted P values were calculated by log-rank test (mutated vs. unmutated subgroup). Due to no events in OS of MYD88 mutated subgroup no odds ratio can be delineated.
Supp. figure 4: Kaplan-Meier estimates of PFS (left) and OS (right) according to the number of mutated genes for the total patient cohort. Subgroups affected by 2 or more mutated genes are depicted by red lines, the subgroup with one mutated gene by yellow lines and wild type patients by dark blue lines. (n=383)
Supp. figure 5: Kaplan-Meier estimates of PFS for subgroups defined by ATM (left) and BIRC3 (right) mutations and co-occurrence of 11q deletion. Mutation status is depicted by line color, 11q status by line structure. P value for log-rank (mutated vs. unmutated subgroup) is denoted for each subgroup.
Supp. figure 6) Allelic fraction of mutation within different genes. A) Each data point corresponds to the VAF of one patient, the lines depict mean allelic fractions within mutated subgroups. B) Kaplan-Meier estimates for PFS for SF3B1 (left) and NOTCH1 (right) mutations according to clone size (<\> 10%VAF). Wildtype is coded blue, patients with only minor mutations (VAF<10%) in yellow, and patients with a major mutation (VAF>10%) in grey. 3’UTR mutations were not considered as the assessment via Sanger sequencing does not allow to determine exact VAF and to detect minor variants.
Supp. figure 7) Kaplan-Meier estimates for PFS for NOTCH1 mutations with different variant allele frequencies. For O-CHL treated patients major NOTCH1 mutations (>40% VAF) have short PFS, while with CHL therapy none of the NOTCH1 mutated subgroups associated with adverse outcome. 3’UTR mutations were not considered, as the assessment via Sanger sequencing does not allow detecting minor variants.
Supp. figure 8) Kaplan-Meier estimates for PFS (upper row) and OS (lower row) for mutated TP53 (a), SF3B1 (b), NOTCH1 (c) and NOTCH1 coding mutations with high allele frequency ("mut>40%coding") for O-CHL and CHL. For NOTCH1 mut>40%coding 3'UTR mutations were not considered as the assessment via Sanger sequencing does not allow to determine exact VAF.