**[Supplementary Appendix](https://www.nejm.org/doi/suppl/10.1056/NEJMoa1809944/suppl_file/nejmoa1809944_appendix.pdf)**

**Table 1.** Response definition for any TKI first line

|  |  |  |  |
| --- | --- | --- | --- |
| **Time** | **Optimal response** | **Warning** | **Failure** |
| **Baseline** |  | High riskMajor route CCA/ Ph+ |  |
| **3 months** | BCR-ABL ≤ 10% \*Ph ≤ 35% (PCyR) | BCR-ABL > 10% \*Ph+ 36-95% | No CHR \*Ph+ > 95% |
| **6 months** | BCR-ABL < 1% \*Ph+ 0% (CCyR) | BCR-ABL 1-10% \*Ph+ 1-35% | BCR-ABL >10% \*Ph+ > 35% |
| **12 months** | BCR-ABL ≤ 0.1% \* (MMR) | BCR-ABL 0.1-1% | BCR-ABL >1% \*Ph+ > 0% |
| **Anytime** | MMR or better | CCA/Ph- (7, or 7q-) | Loss of CHRLoss of CCyRLoss of MMR (confirmed in 2 consecutive test)MutationsCCA/Ph+ |

**Table 2.** Response definition to second line therapy in case of failure imatinib

|  |  |  |  |
| --- | --- | --- | --- |
| **Time** | **Optimal response** | **Warning** | **Failure** |
| **Baseline** |  | No CHRLoss of CHR on imatinibLack of CCyR to 1st line TKIHigh risk |  |
| **3 months** | BCR-ABL ≤ 10% \*Ph < 65%  | BCR-ABL > 10% \*Ph+ 65-95% | No CHR orPh+ > 95% orNew mutations |
| **6 months** | BCR-ABL ≤ 10% \*Ph+ <35% (PCyR) | BCR-ABL ≤ 10% \*Ph+ 35-65% | BCR-ABL >10% \*Ph+ > 65% \*New mutations  |
| **12 months** | BCR-ABL <1% \* Ph+ 0 (CCyR) | BCR-ABL 1-10% \*Ph+ 1-35% | BCR-ABL >1% \*Ph+ > 35%\*New mutations |
| **Anytime** | MMR or better | CCA/Ph- (07, or 7q-) orBCR-ABL > 0.1% | Loss of CHRLoss of CCyRLoss of MMR (confirmed in 2 consecutive test)MutationsCCA/Ph+ |

\*And/Or CCA: Clonal chromosome abnormal

**Table 3.** Risk CML-Related Death

| **Variables** | **Total****(N=150)** | **Event****(N=13)** | **95% CI** | **Log rank test****(p-value)** | **Univariable Analyses** | **Multivariable Analyses** |
| --- | --- | --- | --- | --- | --- | --- |
| **HR** | **95%CI** | **p-value** | **HR** | **95%CI** | **p-value** |
| Sex |  |  |  | 0.968 |  |  |  |  |  |  |
| ·       Female | 68(45.33%) | 6(46.15%) | 0.56-2.78 |  | Ref. |  |  |  |  |  |
| ·       Male | 82(54.67%) | 7(53.85%) | 0.56-2.50 |  | 0.98 | 0.33-2.91 | 0.970 |  |  |  |
| Age | 54.34±16.47 | 61.08± 22.78 | 0.71-2.10 |  | 1.01 | 0.99-1.06 | 0.220 |  |  |  |
| Age of Diagnosis | 45.99±15.77 | 51.15±22.73 | 0.71-2.10 |  | 1.02 | 0.99-1.06 | 0.180 |  |  |  |
| ECOG |  |  |  | 0.002 |  |  |  |  |  |  |
| ·       ECOG 0 - 1 | 133(88.67%) | 8(61.54%) | 0.43-1.70 |  | Ref. |  |  | Ref. |  |  |
| ·       ECOG 2 - 4 | 17(11.33%) | 5(38.46%) | 1.61-9.35 |  | 5.16 | 1.66-15.97 | 0.004 | 4.69 | 1.48-14.87 | 0.009 |
| Underlying Disease |  |  |  | 0.210 |  |  |  |  |  |  |
| ·       No | 94(62.67%) | 10(76.92%) | 0.83-2.85 |  | Ref. |  |  |  |  |  |
| ·       Yes | 56(37.33%) | 3(23.08%) | 0.23-2.23 |  | 0.44 | 0.12-1.62 | 0.220 |  |  |  |
| Diabetes Mellitus | 7(12.50%) | 0(0%) | - | 0.360 | - | - | - |  |  |  |
| Hypertension | 19(33.93%) | 2(15.38%) | 0.38-6.10 | 0.750 | 1.27 | 0.28-5.76 | 0.760 |  |  |  |
| Dyslipidemia | 12(21.43%) | 1(7.69%) | 0.16-8.26 | 0.900 | 0.88 | 0.11-6.80 | 0.900 |  |  |  |
| Chronic kidney disease | 4(7.14%) | 0(0%) | - | 0.460 | - | - | - |  |  |  |
| Coronary artery disease | 2(3.57%) | 0(0%) | - | 0.600 | - | - | - |  |  |  |
| Cerebrovascular disease | 5(8.93%) | 1(7.69%) | 0.36-18.13 | 0.390 | 2.38 | 0.31-18.35 | 0.410 |  |  |  |
| Other | 38(67.86%) | 2(15.38%) | 0.18-2.92 | 0.390 | 0.52 | 0.12-2.35 | 0.400 |  |  |  |
| CML Phase |  |  |  | 0.020 |  |  |  |  |  |  |
| ·        Chronic | 136(90.67%) | 10(76.92%) | 0.56-1.92 |  | Ref. |  |  |  |  |  |
| ·        Accelerated | 8(5.33%) | 3(23.08%) | 1.58-15.21 |  | 4.75 | 1.30-17.30 | 0.018 |  |  |  |
| ·        Blast | 6(4%) | 0(0%) | - |  | - | - | - |  |  |  |
| Ph Chromosome study method |  |  |  |  |  |  |  |  |  |  |
| ·        Cytogenetic study | 149(93.33%) | 12(92.31%) | 0.64-2.00 | 0.030 | 0.14 | 0.02-1.12 | 0.060 |  |  |  |
| ·        FISH | 1(0.67%) | 1(7.69%) | 1.35-68.18 | 0.030 | 7.13 | 0.89-56.87 | 0.060 |  |  |  |
| Sokal score |  |  |  | 0.050 |  |  |  |  |  |  |
| ·        Low | 6(4%) | 1(7.69%) | 0.24-12.01 |  | Ref. |  |  |  |  |  |
| ·        Intermediate | 60(40%) | 1(7.69%) | 0.33-1.66 |  | 0.13 | 0.01-2.13 | 0.150 |  |  |  |
| ·        High | 84(56%) | 11(84.62%) | 1.04-3.41 |  | 1.11 | 0.14-8.62 | 0.920 |  |  |  |
| ELTS score |  |  |  | 0.020 |  |  |  |  |  |  |
| ·        Low | 53(35.33%) | 3(23.08%) | 0.24-2.28 |  | Ref. |  |  |  |  |  |
| ·        Intermediate | 42(28%) | 1(7.69%) | 0.05-2.27 |  | 0.45 | 0.05-4.34 | 0.490 |  |  |  |
| ·        High | 55(36.67%) | 9(69.23%) | 1.34-4.97 |  | 3.6 | 0.97-13.33 | 0.060 |  |  |  |
| Treat |  |  |  | 0.000 |  |  |  |  |  |  |
| ·        1st line Imatinib | 94(62.67%) | 1(7.69%) | 0.02-1.04 |  | Ref. |  |  |  |  |  |
| ·        2nd line Nilotinib | 36(24.00%) | 1(7.69%) | 0.53-2.65 |  | 2.71 | 0.17-43.52 | 0.480 |  |  |  |
| ·        3rd line Dasatinib | 20(13.33%) | 11(84.62%) | 5.17-16.85 |  | 74.18 | 9.35-588.70 | 0.000 |  |  |  |
| Time to MMR |  |  |  | 0.001 |  |  |  |  |  |  |
| ·        ≤ 15months | 88(58.67%) | 3(2308%) | 0.14-1.39 |  | Ref. |  |  | Ref. |  |  |
| ·        > 15months | 62(41.33%) | 10(76.92%) | 1.35-4.65 |  | 6.32 | 1.71-23.29 | 0.006 | 6.00 | 1.60-22.48 | 0.008 |
| Time to CCyR |  |  |  | 0.000 |  |  |  |  |  |  |
| ·        ≤ 12months | 88(58.67%) | 0(0%) | - |  | Ref. |  |  |  |  |  |
| ·        > 12months | 62(41.33%) | 13(100%) | 1.81-5.38 |  | - | - | - |  |  |  |

**Table 4.** Risk Factors of MMR.

| **Variables** | **Total****(N=150)** | **Event****(N=87)** | **95% CI** | **Log rank test****(p-value)** | **Univariable Analyses** |
| --- | --- | --- | --- | --- | --- |
| **HR** | **95%CI** | **p-value** |
| Sex |  |  |  | 0.364 |  |  |  |
| ·       Female | 68(45.33%) | 41(47.13%) | 20.34 – 37.52 |  | Ref. |  |  |
| ·       Male | 82(54.67%) | 46(52.87%) | 17.57 – 31.31 |  | 0.82 | 0.54 – 1.26 | 0.369 |
| Age | 54.34±16.47 | 51.95±15.21 | 20.46 – 31.15 |  | 0.10 | 0.98 – 1.01 | 0.428 |
| Age of Diagnosis | 45.99±15.77 | 43.46 ± 14.81 | 20.46 – 31.15 |  | 0.99 | 0.98 – 1.01 | 0.353 |
| ECOG |  |  |  | 0.012 |  |  |  |
| ·       ECOG 0 - 1 | 133(88.67%) | 83(95.40%) | 24.63 – 37.88 |  | Ref. |  |  |
| ·       ECOG 2 - 4 | 17(11.33%) | 4(4.60%) | 2.06 – 14.63 |  | 0.30 | 0.11 – 0.81 | 0.018 |
| Underlying Disease |  |  |  | 0.811 |  |  |  |
| ·       No | 94(62.67%) | 58(66.67%) | 18.17-30.39 |  | Ref. |  |  |
| ·       Yes | 56(37.33%) | 29(33.33%) | 20.63-42.71 |  | 1.06 | 0.68-1.65 | 0.813 |
| Diabetes Mellitus | 7(12.50%) | 3(3.45%) | 11.21-107.79 | 0.886 | 0.92 | 0.29 – 2.91 | 0.886 |
| Hypertension | 19(33.93%) | 9(10.34%) | 16.36-60.43 | 0.660 | 1.17 | 0.58 – 2.33 | 0.663 |
| Dyslipidemia | 12(21.43%) | 6(6.90%) | 13.67 – 67.74 | 0.519 | 1.31 | 0.57 – 3.00 | 0.523 |
| Chronic kidney disease | 4(7.14%) | 2(2.30%) | 10.64 – 170.11 | 0.881 | 1.11 | 0.27-4.53 | 0.882 |
| Coronary artery disease | 2(3.57%) | 1(1.15%) | 6.02 – 303.62 | 0.970 | 1.04 | 0.144 – 7.50 | 0.969 |
| Cerebrovascular disease | 5(8.93%) | 2(2.30%) | 4.26 – 68.18 | 0.828 | 0.86 | 0.21 – 3.49 | 0.830 |
| Other | 38(67.86%) | 21(24.14%) | 19.17 – 45.09 | 0.934 | 1.02 | 0.62 – 1.67 | 0.080 |
| CML Phase |  |  |  | 0.198 |  |  |  |
| ·        Chronic | 136(90.67%) | 80(91.95%) | 22.68 – 35.16 |  | Ref. |  |  |
| ·        Accelerated | 8(5.33%) | 2(2.30%) | 0.94 – 15.02 |  | 0.32 | 0.08 – 1.30 | 0.111 |
| ·        Blast | 6(4%) | 5(5.75%) | 26.04 – 150.31 |  | 1.29 | 0.52 – 3.20 | 0.583 |
| Ph Chromosome study method |  |  |  |  |  |  |  |
| ·        Cytogenetic study | 149(93.33%) | 87(100%) | 20.54 – 31.26 | 0.404 | - | - | - |
| ·        FISH | 1(0.67%) | 0(0%) | - | 0.404 | - | - | - |
| Sokal score |  |  |  | 0.107 |  |  |  |
| ·        Low | 6(4%) | 2(2.30%) | 2.20 – 35.18 |  | Ref. |  |  |
| ·        Intermediate | 60(40%) | 40(45.98%) | 30.02 – 55.79 |  | 2.88 | 0.70 – 11.93 | 0.144 |
| ·        High | 84(56%) | 45(51.72%) | 14.99 – 26.90 |  | 2 | 0.48 – 8.24 | 0.339 |
| ELTS score |  |  |  | 0.219 |  |  |  |
| ·        Low | 53(35.33%) | 35(40.23%) | 24.82 – 48.14 |  | Ref. |  |  |
| ·        Intermediate | 42(28%) | 22(25.29%) | 15.82 – 36.49 |  | 0.67 | 0.39 – 1.15 | 0.148 |
| ·        High | 55(36.67%) | 30(34.48%) | 13.82 – 28.28 |  | 0.69 | 0.42 – 1.13 | 0.146 |
| Treat |  |  |  | 0.000 |  |  |  |
| ·        1st line Imatinib | 94(62.67%) | 86(98.85%) | 46.12 – 70.38 |  | Ref. |  |  |
| ·        2nd line Nilotinib | 36(24.00%) | 0(0%) | - |  | - | - | - |
| ·        3rd line Dasatinib | 20(13.33%) | 1(1.15%) | 0.12 – 6.02 |  | 0.02 | 0.003 – 0.16 | 0.000 |

**Table 5.** Risk Factors of CCyR.

| **Variable** | **Total****(N=150)** | **Event****(N=133)** | **95% CI** | **Log rank test****(p-value)** | **HR** | **95%CI** | **p-value** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sex |  |  |  | 0.101 |  |  |  |
| ·       Female | 68(45.33%) | 64(48.12%) | 49.44-80.70 |  | Ref. |  |  |
| ·       Male | 82(54.67%) | 69(51.88%) | 32.09-51.44 |  | 0.75 | 0.54 – 1.06 | 0.105 |
| Age | 54.34±16.47 | 54.46±16.31 | 41.38-58.14 |  | 1.00 | 0.99 – 1.00 | 0.330 |
| Age of Diagnosis | 45.99±15.77 | 45.95 ± 15.44 | 41.38-58.14 |  | 1.00 | 0.99 – 1.00 | 0.392 |
| ECOG |  |  |  | 0.057 |  |  |  |
| ·       ECOG 0 - 1 | 133(88.67%) | 120(90.23%) | 48.33 – 69.11 |  | Ref |  |  |
| ·       ECOG 2 - 4 | 17(11.33%) | 13(9.77%) | 11.88 – 35.25 |  | 0.45 | 0.25 – 0.80 | 0.007 |
| Underlying Disease |  |  |  | 0.726 |  |  |  |
| ·       No | 94(62.67%) | 81(60.90%) | 35.63 – 55.07 |  | Ref. |  |  |
| ·       Yes | 56(37.33%) | 52(39.10) | 44.88 – 77.30 |  | 1.06 | 0.75 – 1.51 | 0.728 |
| Diabetes Mellitus | 7(12.50%) | 7(9.26%) | 34.40 – 151.37 | 0.810 | 1.1 | 0.51 – 2.35 | 0.812 |
| Hypertension | 19(33.93%) | 18(13.53%) | 39.99 – 100.75 | 0.741 | 1.08 | 0.660 – 1.789 | 0.743 |
| Dyslipidemia | 12(21.43%) | 11(8.27%) | 29.58 – 96.46 | 0.980 | 1.01 | 0.54 – 1.86 | 0.981 |
| Chronic kidney disease | 4(7.14%) | 4(3.01%) | 28.87 – 204.99 | 0.817 | 1.12 | 0.415 – 3.044 | 0.819 |
| Coronary artery disease | 2(3.57%) | 2(1.50%) | 13.91-222.46 | 0.913 | 0.93 | 0..229 – 3.747 | 0.914 |
| Cerebrovascular disease | 5(8.93%) | 4(3.01%) | 11.19 – 79.43 | 0.475 | 0.7 | 0.26 – 1.89 | 0.480 |
| Other | 38(67.86%) | 35(26.32%) | 41.89-81.25 | 0.736 | 1.07 | 0.73 – 1.57 | 0.738 |
| CML Phase |  |  |  | 0.130 |  |  |  |
| ·        Chronic | 136(90.67%) | 121(90.98%) | 43.51 – 62.13 |  | Ref. |  |  |
| ·        Accelerated | 8(5.33%) | 6(4.51%) | 7.96 – 36.42 |  | 0.51 | 0.22 – 1.17 | 0.110 |
| ·        Blast | 6(4%) | 6(4.51%) | 59.27 – 293.68 |  | 1.59 | 0.70 – 3.64 | 0.273 |
| Ph Chromosome study method |  |  |  |  |  |  |  |
| ·        Cytogenetic study | 149(93.33%) | 132(99.25%) | 41.60 – 58.51 | 0.534 | 1.84 | 0.26 – 13.22 | 0.543 |
| ·        FISH | 1(0.67%) | 1(0.75%) | 3.90 – 196.73 | 0.534 | 0.54 | 0.08 – 3.89 | 0.543 |
| Sokal score |  |  |  | 0.126 |  |  |  |
| ·        Low | 6(4%) | 5(3.76%) | 9.40 – 54.28 |  | Ref. |  |  |
| ·        Intermediate | 60(40%) | 56(42.11%) | 55.44 – 93.61 |  | 1.85 | 0.74 – 4.64 | 0.189 |
| ·        High | 84(56%) | 72(54.14%) | 33.36 – 52.96 |  | 1.35 | 0.54 – 3.34 | 0.521 |
| ELTS score |  |  |  | 0.658 |  |  |  |
| ·        Low | 53(35.33%) | 47(35.34%) | 37.73 – 66.84 |  | Ref. |  |  |
| ·        Intermediate | 42(28%) | 39(29.32%) | 44.12 – 82.65 |  | 0.96 | 0.63 – 1.47 | 0.855 |
| ·        High | 55(36.67%) | 47(35.34%) | 31.25 – 55.37 |  | 0.84 | 0.56 – 1.25 | 0..385 |
| Treat |  |  |  | 0.000 |  |  |  |
| ·        1st line Imatinib | 94(62.67%) | 90(67.67%) | 86.86 – 131.30 |  | Ref. |  |  |
| ·        2nd line Nilotinib | 36(24.00%) | 34(25.56%) | 33.24 – 65.10 |  | 0.3 | 0.20 – 0.46 | - |
| ·        3rd line Dasatinib | 20(13.33%) | 9(6.77%) | 4.12 – 15.20 |  | 0.82 | 0.04 – 0.17 | - |