Genetic correlates in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with Hyper-CVAD / Hyper-CMAD plus dasatinib or Hyper-CVAD plus ponatinib

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Introduction

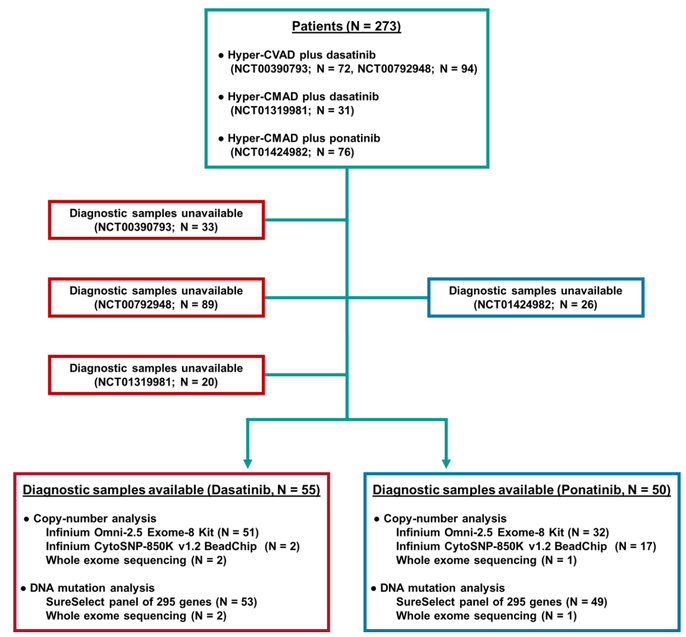
- Genetic abnormalities such as deletions in *IKZF1* (70%), *PAX5* (35%), and *CDKN2A/2B* (30%) detected in Philadelphia chromosome-positive (Ph+) B-ALL.[1)]
- Ph+ B-ALL patients with *IKZF1* deletion have poor prognosis when treated with imatinib- or dasatinib-based regimens.[2)]
- '*IKZF1*^{plus}' (*IKZF1* deletion with additional co-occurring deletion(s)) was also shown to be prognostic in GIMEMA-led trials (dasatinib plus blinatumomab).[3)]
- The molecular determinants for clinical outcomes in ponatinib-treated patients remain unknown.

Aim

We systematically analyzed genetic alterations in adult Ph+ B-ALL patients treated with Hyper-CVAD plus dasatinib,[4)] Hyper-CMAD plus dasatinib,[4)] or Hyper-CVAD plus ponatinib[5)] and investigated the prognostic significance of the genetic alterations.

Methods

Figure 1. CONSORT diagram.



Results

Figure 2. Landscape of genetic alterations in 105 cases of Ph+ B-ALL.

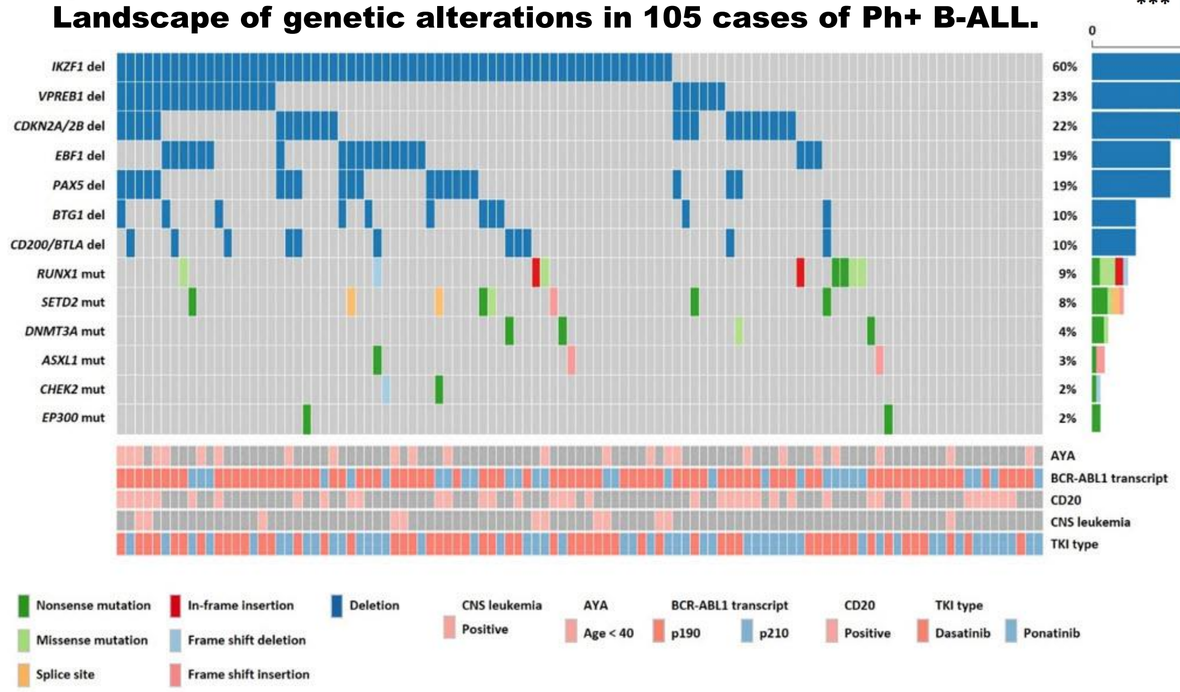


Figure 3. Co-occurrence and exclusiveness of each genetic alteration.

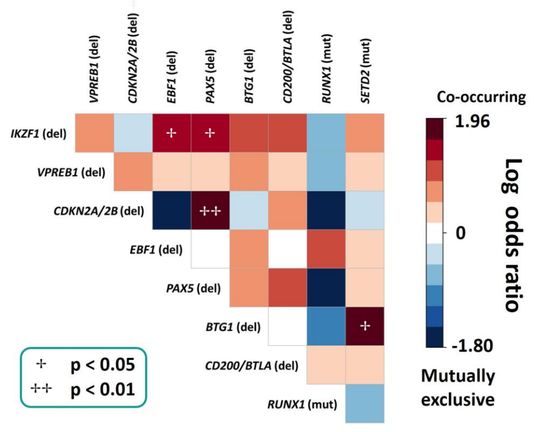
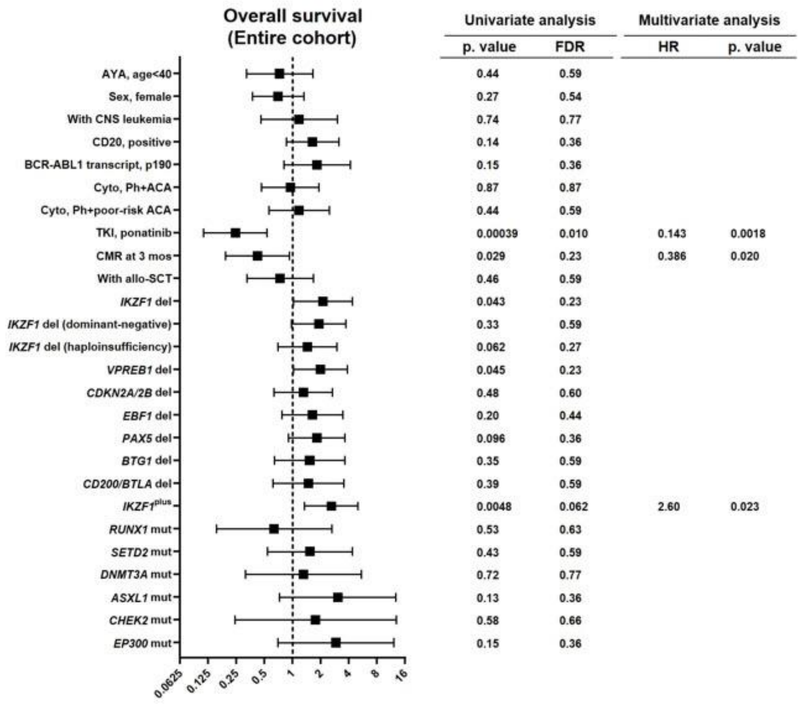


Figure 4. Impact of clinical features and genetic alterations on overall survival.



Abbreviations: CIR, cumulative incidence of relapse, AYA, adolescent and young adult; CNS, central nervous system; cyto, cytogenetics; Ph, Philadelphia chromosome; ACA, additional chromosomal abnormality, TKI, tyrosine kinase inhibitor; MRD, measurable residual disease; mo, month; allo-SCT, allogenic stem cell transplant; del, deletion; mut, mutation; CI, confidence interval; FDR, false discovery rate; HR, hazard ratio.

Figure 5A, B. Impact of *IKZF1* status.

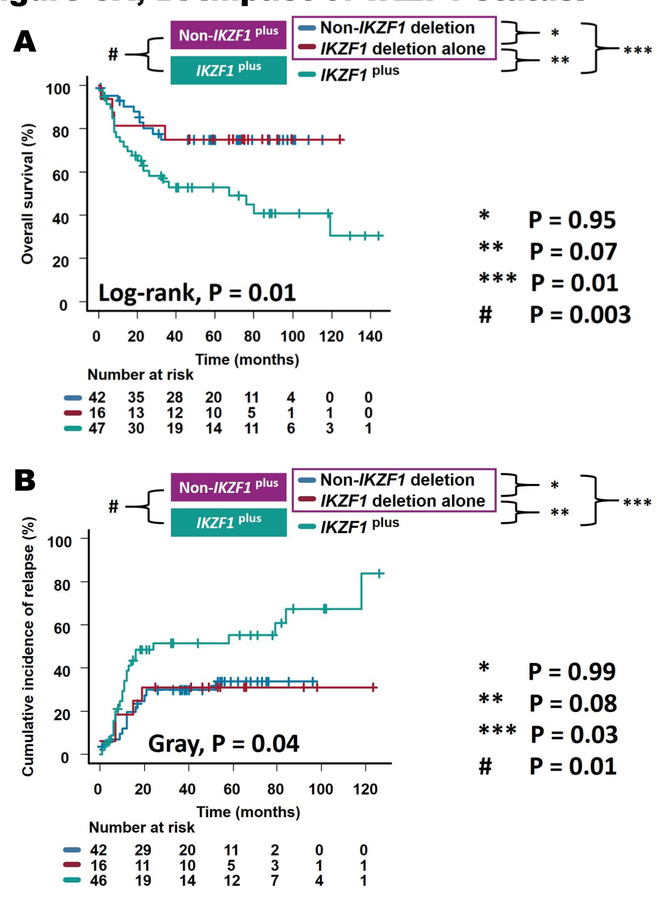
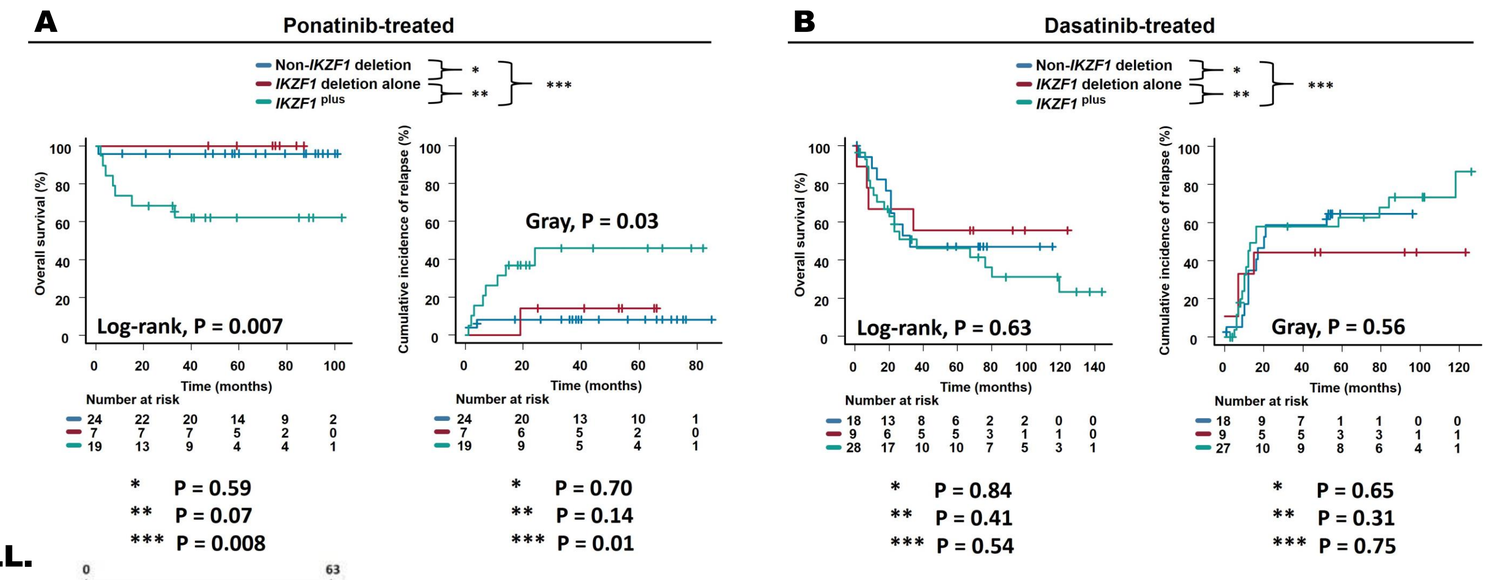


Figure 6A, B. Impact of *IKZF1* status in each cohort (A; ponatinib, B; dasatinib).



Conclusion

IKZF1^{plus} status was an independent prognostic factor for outcome in patients with Ph+ B-ALL treated with Hyper-CVAD plus ponatinib. In contrast, in patients treated with dasatinib-based regimen, the outcomes were poor across all molecular subsets.

Reference

1) Mullighan, C.G. et al. Nature (2007)
2) Martinelli, G. et al. J Clin Oncol (2009)
3) Foà, R. et al. N Engl J Med (2020)
4) Ravandi, F. et al. Blood (2010)
5) Jabbour, E. et al. Lancet Oncol (2015)

Conflict of interest / disclosures

Takeda Pharmaceutical Company (EJ).