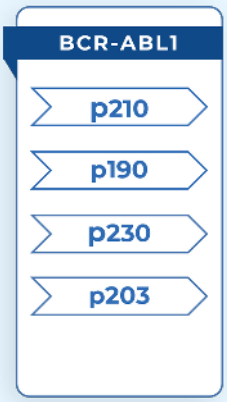
Precipio Spotlight:

Single BCR/ABL1 Fusion Isoform Testing Based on Prior Results Proven Insufficient in Monitoring CML Patient Due to Mutation Co-Expression

Case Background

- 64 YO | Male
- History of CML
- Previous positive p.210 mutation
- Neutrophilic leukocytosis (high eosinophils and neutrophils)

Technology Advantage



Bloodhound BCR::ABL1 Panel

More Case Studies

Abstract

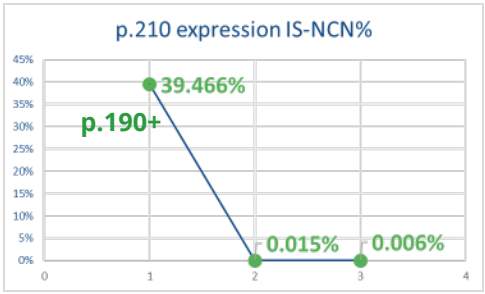
A hallmark of Chronic Myelogenous Leukemia (CML) is the translocation of part of chromosome 9 with chromosome 22, “swapping” DNA across the chromosomes and leading to the formation of oncogene BCR-ABL. Various molecular methods can be used to detect the specific (isoform) oncogene fusions, information that is critical to informing prognostic and therapeutic decisions. Once a specific isoform is identified in a patient, laboratories typically narrow their testing to monitoring only that fusion , to follow patient response and further inform treatment decisions. However, these established fusion isoforms can change over time,. Consequently, narrowly focused monitoring of a single isoform can lead to missed changes in the patient’s oncogene profile, delaying critical care and fast therapeutic intervention. Here we present a case study of a patient tested using a more comprehensive approach to CML patient monitoring by Precipio’s clinical lab that identifies an otherwise-missed isoform change from previous tests, enabling the physician to act quickly to adjust the patient’s treatment plan.

Case Work Up and Findings

- Bloodhound BCR::ABL1 Panel (p.190, p.203, p.210, p.230) run
- Co-expression of p.210 and p.190 breakpoint mutations

Follow Up and Outcome

- Identification of the p.210 and p.190 influenced treatment decisions
- Patient saw a marked decrease in p.210 expression and loss of p.190 expression in subsequent monitoring after treatment



The Precipio Difference:
Clinical monitoring for p210 expression status alone would have been insufficient for monitoring this patient due to the rise in isoform transformation and co-expressions. In a simple workflow, the Bloodhound panel-based approach with broad isoform coverage supports routine monitoring of mutation status as well as detecting isoform transformations and co-expressions when they occur.

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MOLECULAR

Patient: John Doe
DOB/Gender: XX/XX/19XX (64 yrs) - Male
Patient ID/MRN: 12345
Date Collected: XX/XX/20XX XX:XX

Case#: PXX-XXXXX
Status: Final
Report Category:
Detected

Provider: Jane Smith, MD
XYZ Hematology/Oncology
Tel: + 800-123-4567
fax: +800-765-4321

DIAGNOSIS:

Peripheral blood:
- BCR/ABL1 p210 fusion was detected at 39.466% IS-NCN
  BCR/ABL1 p190 fusion was detected.
- ABL1 mutation analysis: No variant detected

INTERPRETATION

Mutations within the BCR/ABL1 kinase domain of patients with chronic myeloid leukemia or acute lymphoblastic leukemia with Philadelphia chromosome are the most commonly identified mechanism associated with resistance to kinase inhibitors. It has been reported that most patients with detectable BCR/ABL1 kinase domain mutations are imatinib resistant or resistant to other kinase inhibitors.

(p190): High Resolution Melt analysis was performed to identify BCR/ABL1 fusion isoform p190 for diagnostic, therapeutic, monitoring and drug-response of Philadelphia chromosome positive leukemic cells. BCR/ABL1 translocations in the major breakpoint cluster region resulting in fusion protein are seen in nearly all cases of chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) and myeloproliferative neoplasms (MPN/MDS).

p190 BCR/ABL1 fusion encodes micro transcripts e19a2 common in Philadelphia-positive B-ALL and has been reported in 1% of CML cases.

(p210 quantification): Molecular analysis was performed to detect and quantify the BCR/ABL1 p210 fusion gene transcripts.

Our results show that the normalized copy number of BCR/ABL1 is 39.466 on the International Scale (%IS-NCN). To monitor patient response to treatment or MRD (Minimal Residual Disease), we recommend evaluating changes from the baseline with time rather than the absolute ratio from a single time point.

To facilitate interlaboratory comparison of findings and the assessment of molecular milestones (major molecular response; MMR), results are reported using the standardized "international scale" (IS) of BCR/ABL1 transcript measurement that has been recommended by an international consensus of CML experts.

The international scale (IS) defines a BCR/ABL1 RNA level as follows:
< 0.05% IS-NCN level : Major Molecular Response (MMR)
> 0.05% IS-NCN <0.15 : Gray zone around MMR cutoff, resulting in inconclusive results.
> 0.15% IS-NCN level : No Major Molecular Response (MMR)

(ABL1): This assay includes screening for targeted ABL1 mutations, which is the most commonly reported imatinib resistance mechanism and also confers resistance to two second generation tyrosine kinase inhibitors, nilotinib and dasatinib. Failure to achieve cytogenetic response in the first six months of therapy in CML patients often reflects the presence of mutations or a high probability that mutations will subsequently be detected.