

BCR/ABL1 Kinase Domain Mutation Analysis

FOR DETECTING POINT MUTATIONS IN IMATINIB-RESISTANT PHILADELPHIA CHROMOSOME-POSITIVE LEUKEMIAS

Clinical Background

- Chronic myelogenous leukemia (CML) is characterized by the presence of the Philadelphia chromosome, the product of the t(9;22)(q34;q11) translocation. This translocation results in the *BCR/ABL* fusion protein with constitutive ABL tyrosine kinase activity. The kinase inhibitor imatinib (STI571, Gleevec®) inhibits ABL kinase activity and is now the standard of care for early phase CML. Prolonged treatment with imatinib can lead to drug resistance, especially in patients with advanced disease. A large portion of resistant patients have acquired point mutations in the ABL kinase domain that renders the kinase resistant to the drug.
- Sites of point mutations in ABL associated with imatinib resistance span the entire kinase domain but often cluster in important hotspots.¹ This test detects greater than 90 percent of ABL mutations that may lead to imatinib resistance, including the important T315I and P-loop mutations. A range of levels of resistance and prognosis has been observed for different mutations.² ABL kinase domain mutations that cause only moderate resistance may be overcome by higher imatinib doses. In addition, several novel ABL kinase inhibitors that are currently in clinical trial still inhibit many of the imatinib-resistant mutants and may become available in the future.³

Indications For Use

The principal use for this test is the detection of point mutations in the kinase domain of the *BCR/ABL* fusion transcript leading to imatinib resistance in Philadelphia chromosome-positive leukemias. It is recommended for CML patients on imatinib therapy that fail or have a suboptimal response, including those with a significant rise in *BCR/ABL* transcript levels (five- to ten-fold increase, documented by more than one test).⁴ The test can detect mutations prior to clinical relapse at a level of at least 1 CML cell in 1,000 normal cells.

Interpretation

- Mutation: Positive for the _____ mutation(s). (Specific mutation will be reported with test results)
- No mutation: No *BCR/ABL* kinase domain mutations detected.
- Not Amplified: No *BCR/ABL* transcripts were detectable by this assay. A "Not Amplified" result does not rule out the presence of *BCR/ABL* transcript at very low levels.

Limitations

Results of this test must always be interpreted in the context of clinicopathologic and other relevant data, and should not be used alone for a diagnosis of malignancy. A negative result does not preclude the presence of *BCR/ABL* mutations in transcripts below the detection limit of this test or the presence of rare mutations not detected by this test. This test does not detect other mechanisms of resistance to imatinib.

Methodology

Total RNA is extracted and cDNA encoding the *BCR/ABL* kinase domain is amplified by RT-PCR and detected by electrophoresis. DNA fragments are then subjected to DNA sequence analysis.

References

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- Nicolini FE, Corm S, Lê QH, Sorel N, Hayette S, et al. Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi(φ)-LMC GROUP). *Leukemia* 2006;20:1061-1066.
- Talpaz M, Shah NP, Kantarjina H, Donato N, Paquette R, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Eng J Med* 2006;354:2594-2596.
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Test Information

0040138

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.