

BCR-ABL1, Major (p210) Quantitative

QUANTITATIVE DETECTION OF BCR-ABL1 RNA WITH THE MAJOR BREAKPOINT (p210)

Clinical Background

- Cases of chronic myelogenous leukemia (CML) and a subset of cases of acute lymphoblastic leukemia (ALL) harbor the t(9;22) (q34;q11) breakpoint, resulting in the *BCR-ABL1* p210 fusion oncogene (Philadelphia chromosome).
- For CML patients, the introduction of tyrosine kinase inhibitor therapy has greatly improved clinical outcome.^{1,2} Quantitative PCR (qPCR)-based monitoring is critical for the assessment of important treatment milestones, such as major molecular response (MMR), and is also helpful for the early detection of emerging drug resistance.^{3,4}
- A standardized reporting scale (international scale; IS) for *BCR-ABL1* p210 mRNA levels has been developed, enabling the comparison of serial data sets regardless of laboratory of origin or specific qPCR test methodology.⁵
- Nearly all CML patients and a subset of Philadelphia chromosome-positive ALL patients exhibit the p210 *BCR-ABL1* fusion resulting from a translocation between *BCR* exons 13 or 14 and *ABL1* exon 2 (e13a2, e14a2). This test is specific for *BCR-ABL1* mRNA with the major breakpoint resulting in the p210 form.

Indications for Ordering

The principal use for this test is to monitor the levels of *BCR-ABL1* fusion mRNA in whole blood from CML and ALL patients with confirmed major breakpoint Ph+ leukemia.

Interpretation

- Results of this test are reported as follows:
 - Detected (percent on international scale)
 - Weakly positive, non-quantifiable (limit of quantification is 0.0069 percent IS)
 - Not detected
- International Scale (IS) reporting
 - An IS of 100 percent is designated as a universal baseline applicable to all patients.
 - A 3 log decrease (0.1 percent) is considered a Major Molecular Response (MMR).
 - Achieving MMR by 18 months of treatment is associated with better outcome.
 - Specimens tested at ARUP prior to May 16, 2011 may be converted to IS (see www.aruplab.com/IS).

Limitations

- Results of this test must always be interpreted in the context of morphologic and other relevant data, and should not be used alone for a diagnosis of malignancy.
- Samples that are negative by this test may still harbor *BCR-ABL1* positive cells at levels below the limit of detection.
- This test does not detect *BCR-ABL1* mRNA with the minor breakpoint (e1a2; p190).

Methodology

- Total RNA is extracted and converted to random-primed cDNA.
- A fragment spanning the *BCR-ABL1* major fusion breakpoint and a normalization control fragment within the *ABL1* cDNA is amplified by quantitative real-time PCR.
- Standard curves are generated with every run, and the normalized copy number (NCN) of *BCR-ABL1/ABL1* is calculated.
- Each run includes IS-calibrated QC reagents, which allows patient data to be efficiently and accurately expressed on the IS.

References

1. O'Brien SG, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348(11):994–1004.
2. Jabbour E, et al. Choosing the best treatment strategy for chronic myeloid leukemia patients resistant to imatinib: weighing the efficacy and safety of individual drugs with BCR-ABL mutations and patient history. *Leukemia* 2010;24(1):6–12.
3. Hughes TP and Branford S. Monitoring disease response to tyrosine kinase inhibitor therapy in CML. *Hematology Am Soc Hematol Educ Program* 2009:477–87.
4. Press RD, et al. Determining the rise in BCR-ABL RNA that optimally predicts a kinase domain mutation in patients with chronic myeloid leukemia on imatinib. *Blood* 2009;114(13):2598–605.
5. Müller MC, et al. Harmonization of molecular monitoring of CML therapy in Europe. *Leukemia* 2009;23(11):1957–63.

Test Information

2005017 *BCR-ABL1 Major (p210), Quantitative*

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

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.