43rd Euro Congress on
Cancer Science & Therapy
May 08-09, 2023
Zurich, Switzerland

Establishment of a NPM1 mutation copy number estimator for Xpert® NPM1 mutation test

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Statement of the problem: The nucleophosmin (NPM1) is the most mutated gene (~30%) in Acute Myeloid Leukemia (AML). Three NPM1 mutations (type A, B and D) represent ~84% in NPM1-mutated AML cases while other uncommon subtypes occupy ~16%. Xpert® NPM1 mutation, an automated cartridge-based test for measuring NPM1 mutation transcript levels (type A, B and D), is standardized to quantify the amount of mutated NPM1 relative to ABL1 control gene based on delta Ct in peripheral blood. Since mutated NPM1 level is crucial for risk assessment, medication selection and ongoing therapeutic monitoring in AML, it is important to obtain the NPM1 mutation Copy Number (CN). The aim of this work is to develop NPM1 mutation CN estimator and to compare %NPM1 mutation/ABL1 reporting between delta Ct-based and CN-based methods.

Methodology and theoretical orientation: Five levels of NPM1 mutations (A, B, D) and ABL1 IVT-RNA panels as well as two lots of Xpert® NPM1 mutation tests were used to generate standard curves for CN and %CN reporting. The cell lysates from cell lines carrying either NPM1 mutation A, B, or D and AML clinical samples containing NPM1 mutations were examined to evaluate the CN and %CN between two lots of the Xpert® NPM1 mutation tests and to compare the delta Ct-based and CN-based methods for reporting %NPM1 mutation/ABL [Figure 1].

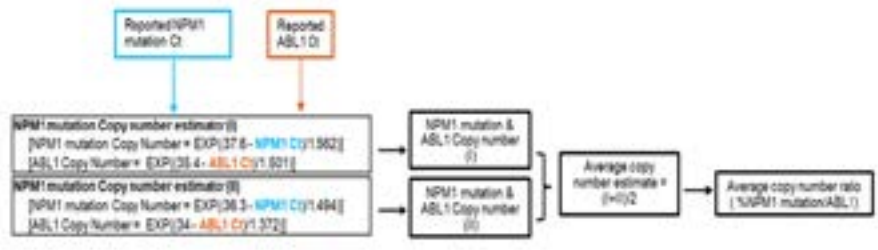

Figure 1. Two sets of NPM1 mutation copy number estimator for Xpert® NPM1 mutation test, which will provide diagnostic and prognostic values for NPM1-mutated AML patients. Enter reported NPM1 mutation Ct and ABL1 Ct into the formulas (I) and (II) to calculate the copy number. Average copy number of NPM1 mutation and ABL1 from both formulas will be utilized in obtaining averaged %NPM1 mutation/ABL1.

Findings: Linearity was demonstrated in Ct vs. CN input for NPM1 mutation and ABL1 with R2 above 0.96 for Lot1 and Lo2. Less than 3-fold difference was exhibited for CN and %CN across two lots of Xpert® NPM1 mutation test. Less than 3-fold difference was observed in %NPM1 mutation/ABL1 reporting between delta Ct-based and CN-based approaches.

Conclusion: An NPM1 mutation copy number estimator for Xpert® NPM1 mutation test was established, which will provide diagnostic and prognostic values for NPM1-mutated AML patients.

Biography

Yan (Amber) Zhao has her expertise in molecular biology, microbiology and cell biology. She has experience in process and assay development. Current research focuses on assay development to provide accurate and high quality IVD products for cancer diagnostic and monitoring.

Received: April 07, 2023; **Accepted**: April 10, 2023; **Published**: May 10, 2023