Annals of Blood Disorders

Review Report Open Access

Article Title: An Uncommon E450G Mutation within the BCR/ABL Kinase Domain in a Chronic Myeloid Leukemia Patient Presenting with Resistance to Imatinib and Nilotinib

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Submission Date: February 16, 2017

Review Status: Revision Required

How to Cite this Report: Tianzhu Zang. ReviewReport for: An Uncommon E450G Mutation within the BCR/ABL Kinase Domain in a Chronic Myeloid Leukemia Patient Presenting with Resistance to Imatinib and Nilotinib. [Version 1, Awaiting Peer Review]. Annals Blood Disord. (2017) 1: 1.1

Review Report

This is a very interesting work which investigated the drug resistant mechanism in CML patient by studying the E450G mutant of ABL kinase domain using structural simulation and secondary and tertiary structural analysis. This work provided the information on the E450G mutation's contribution to the structural change of BCR/ABL tyrosine kinase. A few minor points needed to be addressed as follows:

1. In "Discussion" part, E450G mutation "may lead the conformation of the ABL kinase domain into the closed state;" however, based on Figure 3B and 3C, a more tryptophan- exposed structure could be attained after mutation. Please check it and give a little more explanation on the status of this closed state. Is that possible that this mutant changed the binding affinity with the inhibitors instead of binding site closing? It is important to do the calculation of the hydrogen bonding distance between E450 and K454 and the inhibitor binding affinity with this mutant, and perform the structural simulation of this closed state if it happens in the future.
2. Please describe the full name of CHR and KD and give the correct nomenclature of ANS in this manuscript.
3. Please use the reference number to replace the reference paper "Structure biology contributions to the discovery of drugs to treat chronic myelogenous leukemia" in the method and material part, and describe the manufacturer information for the reagents and instruments.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.