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The Perplexity of Synergistic Duality: Inter-Molecular Mechanisms of Communication in BCR–ABL1

Background: Aberrant and proliferative expression of the oncogene BCR-ABL in bone marrow cells is one of the prime causes of chronic myeloid leukemia (CML). It has been established that the tyrosine kinase domain of the BCR-ABL protein is a potential therapeutic target for the treatment of CML. Although first and second line inhibitors against the enzyme are available, recent studies have indicated that monotherapeutic resistance has become an aggrieved challenge.
Objective/Methods: In recent studies, the dual inhibition of BCR-ABL by Nilotinib and Asciminib was shown to overcome drug resistance. This prompted us to investigate, with the use of computational tools, the molecular dynamics behind this novel drug combination.
Results: Conformational ensemble analysis presented a sustained inactive protein, as the activation loop, inclusive of the characteristic Tyr257, remained in an open position due to the unassailable binding of Asciminib at the allosteric site. Nilotinib also indicated more propitious binding at the catalytic site in the presence of Asciminib, thus exposing new avenues in treating Nilotinib-resistance. This was in countenance with intermolecular hydrogen bond interactions with key binding site residues GLU399, Asn259 and Thr252.
Conclusion: The investigations carried out in this study give rise to new possibilities in the treatment of resistance in CML, as well as assisting in the design of novel and selective inhibitors as dual anti-cancer drugs.

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