Towards the goal of curing CML: discovery of ABL001 a novel allosteric inhibitor of BCR-ABL preventing disease relapse by dual targeting

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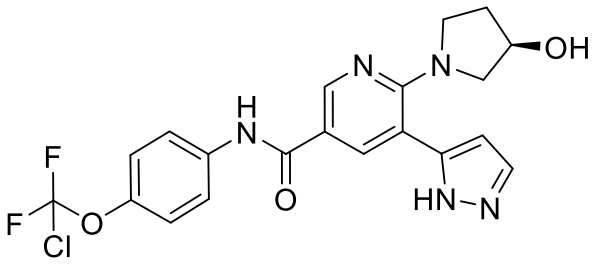
The discovery of ABL001, the first allosteric selective receptor tyrosine kinase inhibitor in Phase I clinical trial for the treatment of patients with chronic myelogenous leukemia (CML) and a subset of acute lymphoblastic leukemia (ALL) will be reported. Two aspects of this ground breaking discovery have significant impacts on cancer research. Firstly; ABL001 is a potent BCR-ABL inhibitor with a novel, allosteric mechanism of action. In contrast to inhibitors such as imatinib and nilotinib that bind to the ATP-site of the kinase domain ABL001 binds to a distinct allosteric site on the kinase domain. Secondly this presents a unique opportunity to treat patients with Ph+ leukemia using a combination of two potent, mechanistically distinct BCR-ABL inhibitors. Pre-clinical efficacy studies have illustrated the potential of this approach with complete regressions being achieved in animals receiving an ABL001/nilotinib combination with no evidence of disease relapse despite treatment being withdrawn. A similar combination approach in the clinic would be anticipated to provide patients with a deeper and more sustained reduction in tumor burden with a reduced risk of relapse. Achieving such a goal would be an important step towards the next paradigm shift providing a cure for patients with CML.



ABL001

Low molecular weight compounds previously identified to bind to the myristoyl-pocket of BCR-ABL, failed to progress to clinical candidates. To develop superior starting points for medicinal chemistry we performed fragment-based screens and the resulting hits were optimized using in silico docking, crystallography and NMR studies. We discovered that myristoyl-pocket binders must induce a critical "bend" in the C-terminal helix for the kinase to form the auto-inhibited conformation.[1] Small molecule medicinal chemistry starting points were discovered using a NMR conformation assay confirming that the molecules could bend the helix. Furthermore the structure-based optimization to improve potency, selectivity and in vivo pharmacokinetics, leading to the discovery of ABL001 will be reported. We will discuss how combinations of ABL001 with the ATP-competitive inhibitor nilotinib, prevents the emergence of drug resistance in vivo. Clinical testing of ABL001 in combination with catalytic-site inhibitors is underway to determine if the pre-clinical observations translate to the clinic and provide potentially curative treatment regimens for patients.

[1] W. Jahnke, R. M. Grotzfeld, X. Pelle, A. Strauss, G. Fendrich, S.W. Cowan-Jacob, S. Cotesta, D. Fabbro, P. Furet, J. Mestan, A. L. Marzinzik, *J. Am. Chem. Soc.* **2010**, 132, 7043-7048.