Discovery of oral PDL1 small molecule inhibitors specifically designed for the treatment of chronic hepatitis B

T WU, S STEVENS, C LIU, H ROOSE, K REKSYTE-MATIENE, E BEHAEGHEL, S MUKHERJEE, S CHANG, R JAINISHNAI, A STOYCEVA1, Q ZHANG1, K GUPTA1, A JEKLE1, J DEVAL1, J SYMONS1, L BLATT1, L BEIGELMAN1, P RABOISSON2, F GONZALVEZ2

1Aligos Therapeutics, Inc. South San Francisco, USA; 2Aligos Belgium BV, Leuven, Belgium, 3Novalix, Leuven Belgium

INTRODUCTION AND OBJECTIVES

In chronic hepatitis B (CHB) patients, upregulation of both PD-1 on HBV-specific T cells and PD1/L1 on liver cells causes T-cell exhaustion and persistent viral infection. Therefore, inhibiting the PD1/PD1/L1 pathway has recently emerged as an attractive therapeutic strategy to reverse immune tolerance in CHB. Seven PDL1/PDL1 antibodies are currently approved as cancer systemic toxicity in CHB patients. Here, we rationally designed liver-targeted oral PDL1 SMi to localize T-cell activation to the liver and thereby potentially mitigate systemic toxicity in CHB patients.

METHODS

Biochemical PD1/PD1/L1 interaction and PDL1 dimenarion were assessed by Alpha.LISA. Cellular activity was measured using a co-culture reporter assay in which TCR-mediated NFAT activity of Jurkat T cells is constitutively inhibited by the engagement of PD1 by PD1/L1 expressing CHO cells. n.a: no activity

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