DEVELOPMENT OF CDK2 INHIBITORS TO OVERCOME PRIMARY AND ACQUIRED RESISTANCE TO CDK4/6 INHIBITION

Claire R. Hall, Angela L. Rauen, Kerry A. Dillon, Anne Y. Lai, Julie E. Pickett, William J. Zuercher, Carrow I. Wells, John E. Bistl, Jay C. Strum

G1 Therapeutics, Inc., Research Triangle Park, NC, USA; Structural Genomics Consortium, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

INTRODUCTION

The cellcycle-dependent kinase (CDK) family of proteins is associated with cell cycle progression and transcriptional regulation. Human adenocarcinomas of the breast are dependent on CDK4/6, and CDK2 and CDK6, with regulatory subunits cyclin D, cyclin E, and cyclin A, respectively, are involved in the cellcycle progression. Although CDK inhibitors are a potential cytototoxic mechanism to treat breast cancer, CDK2 and CDK6 have not been adequately targeted. Inhibitors of CDK2, such as palbociclib, ribociclib, and abemaciclib, have been developed to overcome primary and acquired resistance to CDK4/6 inhibitors. These CDK2 inhibitors can be used as an alternative to CDK4/6 inhibitors for breast cancer treatment and have shown to be active in tumors harboring resistance to CDK4/6 inhibitors.

RESULTS

Engagement Intracellular Kinase Assay results demonstrating potent binding of CDK2/CyclinE by CDK2 inhibitors. A 6-Day CellTiter Glo results for MCF7, H3122, Palbo-CiBl, and MCF7 Palbo-R cell lines treated with CDK2 inhibitors and staurosporine control. MCF7 cells show a 10,000-fold increase in CDK2/CyclinE inhibition and a significant decrease in cell viability when treated with CDK2 inhibitors. Western blot analysis of MCF7, HCC1806, H3122, Hs68, Palbo-CiBl, and Palbo-R cell lines treated with CDK2 inhibitors and staurosporine control. MCF7 cells show a 10,000-fold increase in CDK2/CyclinE inhibition and a significant decrease in cell viability when treated with CDK2 inhibitors.

SUMMARY

Three novel CDK2 inhibitors demonstrate potentially promising method of treating tumors with primary or acquired resistance to CDK4/6 inhibitors. Ongoing and future work for the lead CDK2 inhibitor includes in vitro and in vivo studies evaluating antitumor efficacy in mouse xenograft models.