RXCO05, a Potent and Selective, Reversible BTK Inhibitor Targeting both Wild-type and Mutant C481S BTK with Potent Efficacy in ABC-DLCL Xenograft Mouse Models

Nicolas E. S. Guisoif, Stuart A. Reed, Andrew Thomasof, Victoria Wright, Jennifer A. Woychik, Rose Manto, Fabienne McClean, Valentina Abeld, Diana Castagn, Peggy Goss, Juliete Emmettail, Kelvin Hol, James R. Kelly, James King Touralon, Kristin Lyons, Melanie Muller, Julieen Refurer, Louise Sargent, Fatima Talab, Madita Bingham, Caroline Phillippl and Richard Armef

1Redox Pharma Plc, Alderley Park, United Kingdom; Division of the Department of Internal Medicine, The Ohio State University, Columbus, OH; Comprehensive Cancer Center, Ohio State University, Columbus, OH

INTRODUCTION

BTK is a kinase that is primarily expressed in B-cells and T-cells. It is involved in the regulation of B-cell proliferation, survival, and differentiation. Inhibiting BTK can lead to the inhibition of B-cell proliferation and the induction of apoptosis, making it a potential target for the treatment of B-cell malignancies. However, some patients with B-cell malignancies develop resistance to BTK inhibitors due to the emergence of mutations in BTK. One such mutation is C481S, which confers resistance to BTK inhibitors, including ibrutinib. RXCO05 is a novel BTK inhibitor that is designed to overcome the resistance mediated by the C481S mutation.

METHODS

Kinase binding assays. Enzatech assays were performed using TR-FRET technology. The IC50 value of RXCO05 for BTK was determined using a TR-FRET assay. The IC50 value for ibrutinib was also determined.

Kinase biochemical activity assays. 2,7-cyclo-RThr PRF (676) was used as a substrate. BTK activity was measured using a TR-FRET assay. The IC50 value of RXCO05 for BTK was determined using a TR-FRET assay. The IC50 value for ibrutinib was also determined.

Cellular assay. The inhibition of B-cell proliferation was assessed using the MTT assay. The IC50 value of RXCO05 was determined using the MTT assay.

RESULTS

RXCO05 displays nanomolar affinity and potency in both WT and mutant BTK cells.

RXCO05 has significantly higher affinity and potency compared to ibrutinib in both WT and mutant BTK cells.

RXCO05 is efficacious in an OCl-Ly10 xenograft model.

RXCO05 has significantly higher efficacy compared to ibrutinib in an OCl-Ly10 xenograft model.

CONCLUSION

RXCO05 aims to overcome ibrutinib resistance by targeting both wild type and C481S mutated BTK. Our reversible BTK inhibitor development candidate, RXCO05, is showing promising activity in vitro and in vivo. Further studies are currently ongoing in advanced preclinical and clinical development.