Targeting Ibrutinib-Resistant BTK-C481S Mutation with ARQ 531, a Reversible Non-Covalent Inhibitor of BTK

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BACKGROUND

Ibrutinib is a potent and selective BTK inhibitor and has demonstrated clinical activity in diseases driven by BTK activation. However, resistance to ibrutinib is common, and BTK-C481S is the single most frequent mechanism of resistance. ARQ 531 is a non-covalent, selective BTK inhibitor with improved preclinical and clinical activity compared to ibrutinib.

MATERIALS AND METHODS

Cell lines sensitive to ibrutinib were treated with varying concentrations of ibrutinib or ARQ 531, and cell viability was measured. Kinase activity was assessed using a novel assay that detects both wild-type and C481S mutant BTK activity. Pharmacokinetics were studied in monkeys and dogs. Animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC).

RESULTS

ARQ 531 suppresses BTK signaling pathways in B-cell lines resistant to ibrutinib.

ARQ 531 inhibits proliferation of malignant cells both sensitive and resistant to ibrutinib.

ARQ 531 is efficacious in collagen induced arthritis model.

CONCLUSIONS

ARQ 531 is a potent and selective BTK inhibitor that suppresses the wild-type and C481S mutant BTK in vitro and in vivo. ARQ 531 demonstrates activity in a single-dose and chronic administration model, with improved PK profile compared to ibrutinib. ARQ 531 is therefore a promising candidate for the treatment of BTK-driven diseases, including BTK-resistant malignancies.