BIIB024, a potent pan-Raf kinase inhibitor for melanoma and solid tumors

Brian Elenbaas, Lalita Singh, Antonio Boccia, Patrick Cullen, Hairuo Peng, Ellen Rohde, Brian Raimondo, Gnanasambandam Kumaravel, Ingrid Joseph

Biogen Idec, Inc. Cambridge, MA and 1San Diego, CA; 2Sunesis Pharmaceuticals, South San Francisco, CA

Abstract

Introduction

The Raf kinases (A-Raf, B-Raf and C-Raf) are key regulators of cell proliferation and survival that control signaling through the Raf/Raf/MAPK pathway, comprising of Raf, MEK and ERK. This pathway is frequently deregulated in cancer by mutations, leading to increased cell proliferation and survival. In particular, Ras oncogenes are mutated in 25% of all cancers and B-Raf is mutated in 7% of all cancers, driving 30% of melanoma. B-Raf’s primary target is B-Raf MAPK pathway and Cancer

B-Raf mutant cell lines are the most sensitive to BIIB024 similar to other cancers with B-Raf kinase inhibitors. A subset of B-Raf wild-type lines is sensitive to BIIB024.

B-Raf mutant melanoma tumors remain sensitive to a 2nd dosing cycle of BIIB024.

Biological Background

BIIB024 is a potent, oral pan-Raf kinase inhibitor being developed for the treatment of melanoma and solid tumors. BIIB024 potently inhibits the B-Raf kinase and the wild-type A-Raf, C-Raf kinases in bioassays in a dose-dependent manner. To determine the selectivity of the compound against a panel of 222 unique human kinases, BIIB024 inhibited a small subset of B-Raf, A-Raf, and C-Raf kinases with a half-maximal inhibitory concentration (IC50) of ≤ 3 μM. The selectivity profile of BIIB024 is similar to that of the Raf inhibitor sorafenib.

BIIB024 inhibits a small but important subset of kinases in a similar range as Raf kinases (IC50 1-50 nM).

BIIB024 is efficacious in a B-Raf mutant and wild-type tumor models, consistent with the in vitro sensitivity data.

Material and Methods

Biochemical Kinase Selectivity

†-BIIB024 inhibits a small subset of kinases in a similar range as Raf kinases (IC50 1-50 nM).

BIIB024 shows efficacy in the B-Raf mutant/B-Raf wild-type melanoma model SK-MEL-2 at 25 mg/kg, QDx21, PO.

BIIB024 is efficacious in the B-Raf mutant/B-Raf wild-type melanoma model SK-MEL-2 at 25 mg/kg, QDx21, PO.

BIIB024 causes significant efficacy at doses ranging from 6-50 mg/kg administered orally (PO) on a daily (QD) dosing schedule (p<0.0001 from days 11-32).

BIIB024 inhibits a small but important subset of kinases in a similar range as Raf kinases (IC50 1-50 nM).