

b-Raf) and CRAF (also referred to herein as c-RAF or c- Raf) protein kinases. Throughout the present disclosure, LXH254 is also referred to as a c-RAF (or CRAF) inhibitor or a C-RAF/c-Raf kinase inhibitor. In cell-based assays, LXH254 has demonstrated anti-proliferative activity in cell lines that contain a variety of mutations that activate MAPK signaling. Moreover, LXH254 is a Type 2 ATP -competitive inhibitor of both B-Raf and C-Raf that keeps the kinase pocket in an inactive conformation, thereby reducing the paradoxical activation seen with many B-Raf inhibitors, and blocking mutant RAS-driven signaling and cell proliferation^[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Treatment with LXH254 (Compound A) generates tumor regression in several KRAS-mutant models including the NSCLC-derived Calu-6 (KRAS Q61K) and NCI-H358 (KRAS G12C). LXH254 exhibits efficacy in numerous MAPK-driven human cancer cell lines and in xenograft tumors representing model tumors harboring human lesions in KRAS, NRAS and BRAF oncogenes ^[1].

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PROTOCOL

Animal Administration ^[1]

Mice^[1]

SCID beige female tumor-bearing NCI-H358 mice, n=8 per group, are randomized into 3 groups 14 days post tumor cell inoculation with an average tumor volume range of 259.44- 262.47mm³. Animals are administered an oral dose of either vehicle, LXH254 at 30mg/kg or 200mg/kg daily for 14 consecutive days at a dosing volume of 10 mL/kg of animal body weight during course of treatment. Tumor volumes are measured by digital caliper 3 times a week and body weights of all animals are recorded through the course of treatment.

Female nude tumor bearing Calu6 mice, n=6 per group are randomized into treatment groups on day 17 following tumor implantation, when the average tumor volume is 180 mm³. Treatments with LXH254 are initiated on Day 17 and continued for 16 days. Dosing volume is 10 mL/kg. Tumor volumes are collected at the time of randomization and twice weekly thereafter for the study duration.

Nude female mice tumor bearing NCI-H358, n=8 per group, are randomized into 2 groups with an average tumor volume range of 275.74 mm³. Animals are administered an oral dose of either vehicle or LXH254 at 100 mg/kg daily for 14 consecutive days at a dosing volume of 10 mL/kg of animal body weight during course of treatment. Tumor volumes are measured by digital caliper 3 times a week and body weights of all animals are recorded through the course of treatment^[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Biomed Chromatogr. 2021 Feb;35(2):e4968.

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REFERENCES

[1]. CAPONIGRO, Giordano, et al. THERAPEUTIC COMBINATIONS COMPRISING A RAF INHIBITOR AND A ERK INHIBITOR. WO 2018051306 A1 20180322

Caution: Product has not been fully validated for medical applications. For research use only.

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