Antitumor activity of the selective RAF inhibitor HM95573 in melanoma

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Introduction

The RAF kinase family is a key component of the RAS/RAF/MEK/ERK MAPK signaling pathway that regulates cell proliferation and survival in various tissues. The important role of RAF kinase family in cancer pathophysiology is supported by the prevalence of 40-50% of abnormal BRAF and 15-20% of abnormal NRAS cellular signaling in melanoma cells. HM95573 is developed as a novel therapeutic option for BRAF V600 mutan as well as NRAS mutant melanoma.

- The RAF kinase is a key component of the RAS/RAF/MEK/ERK MAPK signaling pathway that regulates cell proliferation and survival in various tissues.
- The important role of RAF kinase family in cancer pathophysiology is supported by the prevalence of 48-53% of abnormal BRAF and 15-20% of abnormal NRAS cellular signaling in melanoma cells.
- HM95573 is developed as a novel therapeutic option for BRAF V600 mutant as well as NRAS mutant melanoma.

- The RAS/RAF/MEK/ERK signaling pathway is important for the survival and proliferation of tumor cells. Deactivation of the MAPK pathway due to mutations in BRAF and NRAS is considered one of the causes of melanoma.
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- HM95573 is a novel, highly potent RAF kinase inhibitor. Biologically scavenged for over 120 kinase, HM95573 showed the high selectivity toward BRAF mutant and CRAF kinases. The half maximal inhibition concentrations (IC50) of HM95573 against BRAFWT, BRAFV600E and CRAF kinases were 4nM, 7nM and 2nM, respectively. The strongly inhibitory kinase activity toward BRAF enzymes appeared to be CRAF (6nM), DDR1 (11nM), DDR2 (15nM), MEK1 (100nM) and MEK2 (100nM).
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- HM95573 potently inhibited the growth of mutant BRAF melanoma cell lines such as A375 (BRAF V600E) and SK-MEL-28 (BRAF V600E) and of mutant NRAS melanoma cell lines such as SK-MEL-2 (NRAS Q61R) and SK-MEL-30 (NRAS Q61K). In addition, the phosphorylation of MEK and ERK downstream kinases associated with cell proliferation were effectively inhibited kinases subsequent to RAF kinases appeared to be CSF1R (44nM), DDR1 (11nM), DDR2 (26nM), MEK1 >100nM and MEK2 >100nM.
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- Good in vitro DMPK profile and moderate to good systemic exposure in animals. HM95573 offered the opportunity for single agent efficacy in BRAF mutant and RAS mutant cancers. Potential inhibition of RAS-RAF-NEK-ERK signaling in BRAF or NRAS mutated melanoma cell lines.
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- Reduced potential for acquired resistance by HGF exposure and ERK activation in A375 cell line.
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- The antitumor activity of HM95573 was profiled at 1.5μg against 123 kinases using the kinase panel assay operating in the presence of HGF which is known to mediate innate resistance to RAF inhibitors. HM95573 showed the excellent antitumor activity in mouse models xenografted with BRAFV600E and BRAFV600E and CRAF kinases (A375 and SK-MEL-28). Histopathological evaluation of tumors including melanoma in Korea.

- Reduced potential for acquired resistance by HGF exposure and ERK activation in A375 cell line.
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- HM95573 is an orally active, selective and potent 2nd generation RAF inhibitor.
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- Good in vivo ZD6474 profile and moderate to good systemic exposure in animals.
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- Potential for minimized cut SCC side effects and resistance. Currently in phase I clinical trial in patients with advanced solid tumors including melanoma in South Korea.

References
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Antitumor activity of the selective RAF Inhibitor HM95573 in solid tumors and hematologic malignancies

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Abstract

- The RAF kinase is a key component of the RAS/RAF/MEK/ERK signaling pathway that regulates cell proliferation and survival in various tissues.
- The importance of the RAF pathway in cancer pathogenesis is supported by the abnormal BRAF and RAS cellular signaling in various solid tumors.
- HM95573 is developed as a novel therapeutic option for RAS mutant as well as BRAF mutant advanced solid tumors.

Introduction

- HM95573 is an orally active, selective and potent 2nd generation RAF inhibitor.
- Good in vitro DMPK profile and moderate to good systemic exposure in animals.
- Currently in phase I clinical trial in patients with advanced solid tumors.

in-vitro Activity

- Selectivity for other kinases
- Biocatalytic potency (IC50, nM) of HM95573 against BRAF WT, BRAF V600E and CRAF mutant (e.g. IC50: V600E 3nM, CRAF <0.1nM).

in-vivo Efficacy

- Xenograft efficacy study in HBG2 (NRAS, Q61K) HCC cell lines
- Combining with MEKi, 10 mg/kg, BIDx14
- Combination with Capecitabine 3 Combination with MEKi
- Inhibition of MEK and ERK phosphorylation in KRAS mutant cell lines (Calu-6 and HCT-116) and NRAS mutation cell lines (HepG2 and Calu-6).

References

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2. A. Cox and C. Der, Cancer cell, 2012; 21; 147-149.