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J Cancer Sci Ther 2019, Volume 11
DOI: 10.4172/1948-5956-C1-160

32nd Euro Congress on

Cancer Science & Therapy

March 07-08, 2019 | Barcelona, Spain

Small Molecule KRAS Agonist for Mutant KRAS Cancer Therapy

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Lung cancer patients with KRAS mutation(s) have a poor prognosis due in part to the development of resistance to currently available therapeutic interventions. Development of a new class of anticancer agents that directly targets KRAS may provide a more attractive option for the treatment of KRAS-mutant lung cancer. Here we identified a small molecule KRAS agonist, KRA-533, that binds the GTP/GDP-binding pocket of KRAS. *In vitro* GDP/GTP exchange assay reveals that KRA-533 activates KRAS by preventing the cleavage of GTP into GDP, leading to the accumulation of GTP-KRAS, an active form of KRAS. Treatment of human lung cancer cells with KRA-533 resulted in increased KRAS activity and suppression of cell growth. Lung cancer cell lines with KRAS mutation were relatively more sensitive to KRA-533 than cell lines without KRAS mutation. Mutating one of the hydrogen-bonds among the KRA-533 binding amino acids in KRAS (mutant K117A) resulted in failure of KRAS to bind KRA-533. KRA-533 had no effect on the activity of K117A mutant KRAS, suggesting that KRA-533 binding to K117 is required for KRA-533 to enhance KRAS activity. Intriguingly, KRA-533-mediated KRAS activation not only promoted apoptosis but also autophagic cell death. In mutant KRAS lung cancer xenografts and genetically engineered mutant KRAS-driven lung cancer models, KRA-533 suppressed malignant growth without significant toxicity to normal tissues. Thus, the development of this KRAS agonist as a new class of anticancer drug offers a potentially effective strategy for the treatment of lung cancer with KRAS mutation and/or mutant KRAS-driven lung cancer.

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