MK-2206, a Novel Akt Inhibitor, Suppresses Medullary Thyroid Cancer Proliferation Independent of RET

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Introduction

Medullary thyroid cancer (MTC) is a neoplasm arising from calcitonin-producing parafollicular C cells. It is associated with a lower overall survival rate than well-differentiated epithelial thyroid cancers, and, although it represents only 5% of all thyroid cancers, it accounts for more than 13% of deaths from thyroid cancer. Many new therapies proposed for MTC target the RET protein, but the phosphoinositide-3-kinase (PI3K)/Akt pathway upregulation has also been linked to tumor growth in many cancer cell lines. Inhibition of the PI3K/Akt leads to growth suppression in multiple tumor types, including MTC. MK-2206 is a novel orally administered compound that allosterically inhibits Akt phosphorylation at serine 473 and threonine 308 residues. A phase 1 trial showed it can lead to growth suppression in multiple tumors, including MTC. MK-2206 is a novel orally administered compound that allosterically inhibits Akt phosphorylation at serine 473 and threonine 308 residues. A phase 1 trial showed it can be administered safely to humans at clinically effective doses.

Results

**Treatment with MK-2206 inhibits MTC-TT cell growth.** MTT cellular viability assay demonstrates a dose- and time-dependent reduction in TT cell growth over 8 days. All represented doses are MK-2206 in cell media.

![Graph showing MTT cellular viability assay results](Image)

**Mechanisms of Growth Suppression:**

A) Increasing doses of MK-2206 reduce phosphorylation at the serine 473 residue of Akt, with more limited reduction at threonine 308. Levels of total Akt protein remain stable with treatment. B) MTC cells show a dose-dependent decrease in production of ASCL1, with a marginal increase in phosphorylation at serine 473. ASCL1 levels suggest no change in cell cycle signaling. C) Total RET protein levels are stable with MK-2206 treatment. Select phosphorylation residues actually increase with treatment, indicating RET activity is not blocked by MK-2206 treatment.

![Western Blot images showing Akt and RET phosphorylation](Image)

**Conclusions**

- MK-2206 inhibits Akt in medullary thyroid cancer cells, leading to reduction in cell growth.
- Mechanisms are separate from the RET pathway. MK-2206 may be a treatment option for MTCs resistant to RET inhibitors.
- MK-2206 is easy to administer to humans, has been vetted in phase 1 trials, and thus could transition to phase 2 trials once its efficacy is proven for MTC treatment in vivo.

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References