The Glutaminase Inhibitor CB-839 Synergizes with CDK4/6 and PARP Inhibitors in Pre-Clinical Tumor Models

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Many tumor cells utilize the amino acid glutamine to meet the elevated biosynthetic and lipogenic demands of growing solid tumors. The glutaminolytic network produces critical metabolites, such as amino acids, TCA cycle intermediates and nucleotides. We developed CB-839, a potent and orally bioavailable small molecule inhibitor of glutaminase, that blocks production of glutamate and metabolites, such as amino acids, TCA cycle intermediates and nucleotides. CB-839 significantly decreases levels of glutamine-derived metabolites following treatment with CB-839. CB-839 targets a unique node in the glutaminolytic network, the native enzyme glutaminase, which is required for de novo synthesis of glutamate from glutamine. CB-839 synergizes with a CDK4/6 inhibitor to block cell cycle progression and cell proliferation. CB-839 decreases nucleotides in tumor cells, impairing DNA synthesis, and cell cycle progression. CB-839 synergizes with PARP inhibitors to impair DNA synthesis, enhance DNA damage, and block cell proliferation.

Conclusions

- CB-839 decreases nucleotides in tumor cells, impairing DNA synthesis, and cell cycle progression.
- CB-839 synergizes with PARP inhibitors to impair DNA synthesis, enhance DNA damage, and block cell proliferation.
- In vivo, CB-839 in combination with PARP inhibitors demonstrates enhanced anti-tumor activity on colorectal and prostate tumor models.
- CB-839 synergizes with a CDK4/6 inhibitor to block cell cycle progression and cell proliferation.

Summary

CB-839 reduces nucleotides in tumor cells, impairing DNA synthesis, and cell cycle progression. CB-839 synergizes with PARP inhibitors to impair DNA synthesis, enhance DNA damage, and block cell proliferation. CB-839 decreases nucleotides in tumor cells, impairing DNA synthesis, and cell cycle progression. CB-839 synergizes with PARP inhibitors to impair DNA synthesis, enhance DNA damage, and block cell proliferation. CB-839 decreases nucleotides in tumor cells, impairing DNA synthesis, and cell cycle progression. CB-839 synergizes with PARP inhibitors to impair DNA synthesis, enhance DNA damage, and block cell proliferation. CB-839 decreases nucleotides in tumor cells, impairing DNA synthesis, and cell cycle progression. CB-839 synergizes with PARP inhibitors to impair DNA synthesis, enhance DNA damage, and block cell proliferation.