CB-839, a Selective Glutaminase Inhibitor, has Anti-Tumor Activity in Renal Cell Carcinoma and Synergizes with Everolimus and Receptor Tyrosine Kinase Inhibitors


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Abstract

CB-839 Treatment Suppresses the mTOR Pathway

Low-dose cabozantinib (A) dependent on the intensity of TCA flux. Expression of the enzyme pyruvate carboxylase (PC), which converts pyruvate to oxaloacetate, is downregulated in tumors treated with this combination. CB-839 is currently being tested in phase 1 clinical trials of patients with solid and hematologic tumors, and is showing promising clinical activity in combination with everolimus in RCC patients.

Figure 1. CB-839 inhibits tumor cell metabolism. Tumors rely on the metabolism of glucose and glutamine for energy and biosynthesis. CB-839 promotes the use of glucose for energy, as indicated by increased glucose uptake in drug-treated tumors, and inhibits glutaminase activity, as indicated by reduced glutamine uptake in drug-treated tumors. Source: Y. Lin, determination on GLS2.

Clinical Outcome for Patients Treated with CB-839 and Everolimus

- 15 evaluable patients: 12 ccRCC and 3 pRCC
- One PR in a ccRCC patient
- Median PFS for CB-839 plus everolimus treated patients is currently 8.5 months
- Median PFS for everolimus treated RCC patients has been reported to be 3.9* to 4.4^ months

Figure 2. CB-839 shows significant single-agent activity and combines with cabozantinib to produce strong anti-tumor activity. (A) CB-839 has potent anti-proliferative activity in RCC cells that correlate with glutamine dependency. (B) Relative cell growth or cell survival in cells treated with DMSO, CB-839 (1 μM) and cabozantinib (1 μM). Relative cell growth (CB-839) = 0.33.

CB-839 Synergizes with Cabozantinib in RCC cells

Figure 3. CB-839 has potent anti-proliferative activity in RCC cells that correlate with glutamine dependency. (A) Relative cell growth or cell survival in cells treated with DMSO, CB-839 (1 μM) and cabozantinib (1 μM). Relative cell growth (CB-839) = 0.33.

Figure 4. Schematic representation of glutamine metabolism showing experimentally measured metabolites (amino acids, TCA cycle intermediates). CB-839 promotes a consistent metabolic response that includes a suppression of glutamate and downstream metabolites (amino acids, TCA cycle intermediates).

Figure 5. Synergistic anti-proliferative activity and combination with everolimus in RCC cells. (A) Decrease in proliferation of tumor cells treated with DMSO, CB-839 (1 μM), everolimus (1 μM), and both drugs (Combo). Relative cell growth (Combo) = 0.19.

Figure 6. Enhanced in Vivo Efficacy of CB-839 plus Cabozantinib

Figure 7. CB-839 Synergizes with Everolimus in RCC cells

Figure 8. Enhanced in Vivo Efficacy of CB-839 plus Everolimus

Conclusions

- CB-839 potentially inhibits glutaminolysis, proliferation of RCC cell lines and tumor growth in a RCC xenograft mouse model.
- CB-839 synergizes with everolimus and cabozantinib to decrease:
  - Proliferation, signal transduction and metabolism in RCC cells
  - Tumor growth in RCC xenograft mouse models
- Clinical trials of CB-839 in combination with everolimus or cabozantinib are ongoing
- CB-839 in combination with everolimus has efficacy in RCC patients

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