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Telaglenastat (CB-839):

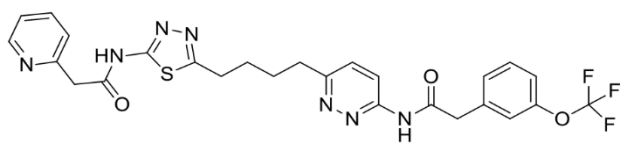
A potent and selective reversible inhibitor of the enzyme glutaminase

What is telaglenastat?

- Telaglenastat is first-in-class, orally bioavailable, **small molecule** allosteric **inhibitor of glutaminase.** It has anti-tumor activity in a number of preclinical models, **both as a monotherapy and in combinations**. Clinical responses have been seen in Phase 1 clinical trials using single agent telaglenastat. Combinations with SOC drugs used to treat RCC, TNBC, NSCLC, melanoma, MM, and AML have been evaluated as part of the Phase 1 and 2 program.
- To date, telaglenastat has been **well tolerated in patients both in a single agent setting and in combination** with SOC.

Telaglenastat: Development Update

- To date, telaglenastat has been given to **over 850 patients**. Telaglenastat is **well tolerated** at doses through **800 mg on the BID** with food schedule and an MTD has not been identified.
- In **Vitro & In Vivo Synergy of teleglenastat and devimistat** in Head and Neck Cancer: The combination of teleglenastat and devimistat demonstrated **significant reductions in cell viability and increased apoptosis** compared to teleglenastat or devimistat alone in HNSCC cell lines. Additionally, this **combination led to significant tumor shrinkage in HNSCC mouse models** when compared to teleglenastat or devimistat alone.
- A preclinical work for the **combination of teleglenastat and devimistat in pancreatic cancer and biliary tract cancer is ongoing.**
- **Phase 1 trial** *(NIH sponsored)* of **telaglenastat, in combination with Sapanisertib** in patients with **Advanced NSCLC** is ongoing. The study is expected to be **completed by September 2023.**
- **A Phase Ib** *(NIH sponsored)* Trial of **telaglenastat with osimertinib** in patients with **EGFR Mutant Stage IV NSCLC** is ongoing. The study is expected to be **completed by June 2024.**



Telaglenastat: Mechanism of Action

- Telaglenastat is a potent, selective, and orally bioavailable inhibitor of both splice variants of glutaminase, that are KGA (kidney glutaminase) and GAC (glutaminase C)
- The first step in glutamine utilization is its conversion to glutamate by the mitochondrial enzyme glutaminase
- Telaglenastat depletes the intracellular pool of glutamate, reducing the availability of glutamate as a precursor for the synthesis of other important molecules
- The reduction in glutamate levels leads to a decrease in the production of glutathione. This sensitizes cancer cells to the damaging effects of reactive oxygen species.
- The inhibition of glutaminase disrupts the production of ATP (adenosine triphosphate) from glutamine metabolism, reducing the energy supply available to cancer cells