GB5121 is a Novel, Highly Potent and Selective CNS-Penetrant BTK Inhibitor for CNS Malignancies

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BACKGROUND

- Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of non-Hodgkin lymphoma that is restricted to the CNS
- Inhibitors of Bruton’s tyrosine kinase (BTK) are approved treatments for several B cell lymphomas, but are characterized by modest selectivity and/or low CNS exposure
- GB5121 is an orally available, selective, irreversible small molecule BTK inhibitor chosen for development based on its potency, selectivity and high CNS exposure
- These features differentiate GB5121 from other BTK inhibitors and support its use in clinical trials for CNS malignancies

Figure 1. BTK inhibition targets a key survival node in PCNSL

RESULTS

- GB5121 demonstrates >50% inhibition of only two kinases besides BTK (TEC and TXK)
- Compared to ibrutinib, GB5121 lacks activity against EGFR, ERBB2 (HER2) and ERBB4 (HER4)

Figure 2. GB5121 is a highly selective BTK inhibitor

- GB5121 is an orally available, selective, irreversible small molecule BTK inhibitor
- Comparative BTK target occupancy of GB5121 and ibrutinib was assessed using biochemical and cell-based assays
- Pharmacokinetic profiles of GB5121 were obtained in multiple species using non-warhead control compounds
- GB5121 demonstrates >50% inhibition of only two kinases besides BTK (TEC and TXK)
- GB5121 lacks activity against EGFR, ERBB2 (HER2) and ERBB4 (HER4)

Figure 3. GB5121 does not inhibit phosphorylation of EGFR in A431 cell line

- Preclinical studies demonstrated GB5121 to exhibit several characteristics differentiating it from approved BTK inhibitors and those currently under clinical investigation, including:
  - rapid equilibrium into the brain
  - superior BTK inactivation rate and brain target occupancy
  - high selectivity over other kinases
  - Excellent brain exposure and selectivity combined with activity against DLBCL cell lines support the use of GB5121 as a novel molecule to treat human primary/secondary CNS lymphoma and primary vitreoretinal lymphoma (NCT05242146)

Figure 4. GB5121 shows potent activity in vitro in diffuse large B cell lymphoma (DLBCL) cell lines regardless of phenotype and mutational profile

- GB5121 demonstrates a 1:1 brain to plasma ratio in non-human primates (n=3) after an IV dose

Figure 5. GB5121 shows superior CNS exposure with lower plasma exposures compared to ibrutinib in naïve mice with intact BBB

- GB5121 is a novel, highly potent and selective CNS-penetrant BTK inhibitor for CNS malignancies

Table 1. BTK enzymatic mechanism of inhibition studies demonstrate properties of an irreversible covalent inhibitor

Table 2. Potency and inactivation kinetics in cells and whole blood

Table 3. GB5121 brain to plasma ratios after single or multiple daily oral (PO) dosing in multiple species

SUMMARY AND CONCLUSIONS

- GB5121 is an orally-available covalent BTK inhibitor that is currently being investigated in a phase 1b/2 trial in patients with relapsed/refractory primary/secondary CNS lymphoma and primary vitreoretinal lymphoma
- Preclinical studies demonstrated GB5121 to exhibit several characteristics differentiating it from approved BTK inhibitors and those currently under clinical investigation, including:
  - rapid equilibrium into the brain
  - superior BTK inactivation rate and brain target occupancy
  - high selectivity over other kinases
- Excellent brain exposure and selectivity combined with activity against DLBCL cell lines support the use of GB5121 as a novel molecule to treat human BTK-driven malignancies including CNS lymphoma

REFERENCES


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