**The novel BCR::ABL1 allosteric inhibitor TERN-701 (HS-10382) is potent against mutations resistant to active site tyrosine kinase inhibitors (TKIs) and acts synergistically with TKIs in BCR::ABL1+ cancer cell lines.**

**1 BACKGROUND**
- Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal translocation between chromosomes 9 and 22, leading to the loss of myb-related autophagy and constitutive activation of the BCR::ABL1 oncogene.
- TERN-701 is a novel allosteric inhibitor of BCR::ABL, optimized for selectivity and pharmacokinetic parameters, that binds the myristate pocket.

**2 METHODS**
- Studies were conducted to characterize the potency, selectivity, and potential of TERN-701 to act synergistically with active site TKIs.

**3 RESULTS**
- TERN-701 inhibited native BCR::ABL1 in vitro biochemical assays with an IC50 = 0.4 nM, and inhibited cell proliferation in a dose- and concentration-dependent manner (IC80 = 0.6 – 15.6 nM (Figure 2A-D), depending on genetic background and BCR::ABL1 mutation status. TERN-701 retained activity against the clinically relevant T315I mutation. With respect to selectivity, in vitro kinase panel, TERN-701 did not inhibit any kinase by >50% at 1 µM, including full-length ABL1 (Figure 2B). TERN-701 was highly potent and selective against only BCR::ABL1+ cell lines in cancer cell line panel, and was more selective than asciminib (Figure 3). In vitro combination studies revealed that TERN-701 works synergistically with multiple TKIs in the K562 cell line, while additivity and weak synergy was observed in the Ku812 cell line (figures 4A & 5 and tables 1 & 2). As assessed using the BLISS model, synergy was strongest at and below the IC50 of each single compound.

**4 CONCLUSION**
- TERN-701 is a potent and selective allosteric inhibitor of BCR::ABL1 in cell-free and cell-based assays, with comparable potency and synergy profiles to that of asciminib while potentially being more selective.
- TERN-701 retains activity against the T315I gatekeeper mutation, which confers resistance to all approved active site TKIs except for ponatinib, which has known safety liabilities.
- A global phase 1 trial assessing safety and initial efficacy of TERN-701 monotherapy is on track to begin by the end of 2023. These data support the continued development of TERN-701 for the treatment of CML through monotherapy and potentially combination approaches.
- TERN-701 is being evaluated in a Ph 1 dose escalation/expansion study as HS-10382 in China.