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604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Tern-701 (HS-10382) Is a Potent Inhibitor of BCR::ABL1 and Is Synergistic with Active Site Tyrosine Kinase Inhibitors

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BACKGROUND Although tyrosine kinase inhibitors (TKIs) targeting the ATP-binding site of the BCR::ABL1 oncoprotein are effective therapeutics for chronic myeloid leukemia (CML), patients often develop drug resistance due to ATP-site mutations that inhibit drug binding. TERN-701 is a potent and highly selective inhibitor of BCR::ABL1 that is designed to bind the allosteric myristoyl site on the kinase, circumventing resistance to active site mutations, with potential for synergistic combination with active site TKIs.

METHODS Competition binding screens were used to assess the selectivity of TERN-701 on more than 450 targets spanning the human kinome. The potency of TERN-701 against the proliferation of wild type and mutant CML cell lines, as well as a panel of 102 cancer cell lines, was assessed using CellTiter-Glo®. Synergy between TERN-701 and active site TKIs was assessed in vitro with interactions quantified using Bliss, combination, and curve-shift analyses. Prospective mutagenesis experiments were conducted by treating BaF/3 cells engineered to overexpress the BCR::ABL1 kinase with various concentrations of both TERN-701 and the TKI imatinib, followed by observation of clonal outgrowth of treated cells over time.

RESULTS We have previously shown that TERN-701 is a potent inhibitor of native CML cell lines such as K562. Here, we show that TERN-701 inhibited cell proliferation in various clinically relevant mutant CML cell lines (including T315I) with IC_{50}s ranging from 5 to 26 nM and 70 to 1200 nM against active site and myristoyl site mutations, respectively. TERN-701 was highly selective for BCR::ABL1, with no appreciable activity (>50%) against >450 purified kinase targets. Against a panel of cancer cell lines, TERN-701 was more selective than the comparator allosteric BCR::ABL1 inhibitor asciminib while maintaining similar potency. *In vitro* combination studies previously revealed that TERN-701 works synergistically with multiple TKIs in the non-mutant K562 cell line. Here, expanded studies using KCL22-s and BCR::ABL1-T315I mutant cell lines identified strong synergistic interactions between TERN-701 and active site TKIs, including ponatinib and dasatinib. Furthermore, prospective mutagenesis studies showed that the combination of TERN-701 and imatinib resulted in greater inhibition of the outgrowth of resistant clones relative to either compound alone.

CONCLUSIONS TERN-701 is a potent and highly selective allosteric inhibitor of BCR::ABL1 that can act synergistically with active site TKIs *in vitro*, even against the T315I gatekeeper mutation that confers resistance to all approved active site TKIs except ponatinib, which has known safety liabilities. These data support the continued development of TERN-701 for the treatment of CML using both monotherapy and combination approaches.

Disclosures M Parsons: *Terns Pharma:* Current Employment, Current equity holder in publicly-traded company. **Jasper:** *Terns Pharma:* Current Employment, Current equity holder in publicly-traded company. **Jones:** *Terns Pharma:* Current Employment, Current equity holder in publicly-traded company.

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