Efficacy of HS-10382 (TERN-701) in tumor xenograft models, a new investigational allosteric ABL1 kinase inhibitor as a potential treatment for CML

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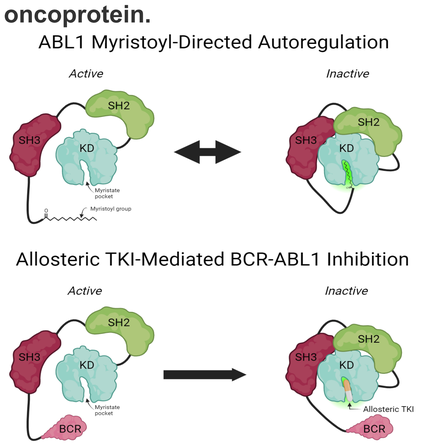
1 BACKGROUND

- Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal translocation between chromosomes 9 and 22, leading to the loss of myristoyl-directed autoregulation and constitutive activation of the BCR-ABL1 oncoprotein.[1,2]
- HS-10382 (TERN-701) is a novel allosteric inhibitor of BCR-ABL1, optimized for selectivity and pharmacokinetic parameters, that binds the myristate pocket.
- TERN-701 retains activity against the BCR-ABL1^{T315I} resistance mutation which confers resistance to all approved active site inhibitors except for ponatinib.[3]

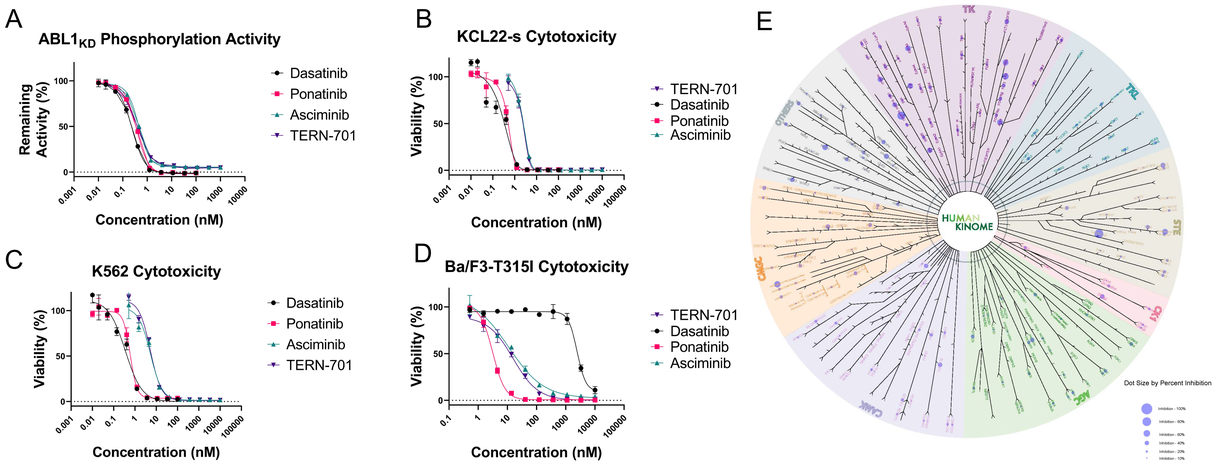
Figure 1. Schematic representation of allosteric inhibition of the BCR-ABL1 oncoprotein.



2 RESULTS

TERN-701 *in vitro* potency and selectivity

A) Inhibition of ABL1 kinase domain activity by TERN-701 and comparator tyrosine kinase inhibitors (TKIs) in a radioactive substrate phosphorylation assay (**TERN-701 IC50 = 0.4 nM**). B,C,D) Anti-proliferation concentration-response curve of KCL22-s, K562, and Ba/F3^{T315I} cells treated with TERN-701 or comparator TKIs (**TERN-701 IC50 = 2.28 nM, 5.25 nM, and 15.60 nM for panels B, C, and D respectively**). TERN-701 demonstrated comparable potency to the control allosteric inhibitor asciminib. Cell viability was assessed using CellTiterGlo. E) TERN-701 was also assessed at 1 µM against a panel of 375 kinases; no kinase, including wild-type ABL1, was inhibited by >50%.

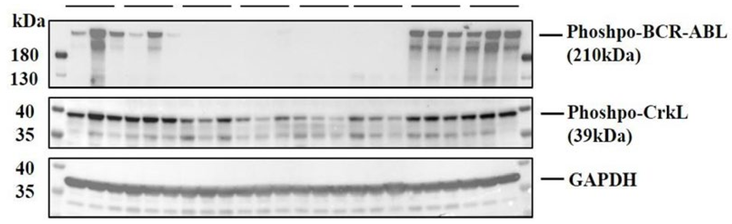


TERN-701 modulation of *in vivo* pharmacodynamic biomarkers

BALB/c nude mice were administered a single dose of TERN-701 p.o. following implantation with KCL22-s xenografts. Tumor tissue and plasma were then collected at the specified time points post-dose to establish a PK/PD relationship. TERN-701 inhibited both BCR-ABL1 autophosphorylation and Crkl (a BCR-ABL1 target protein) phosphorylation in a time-dependent manner.

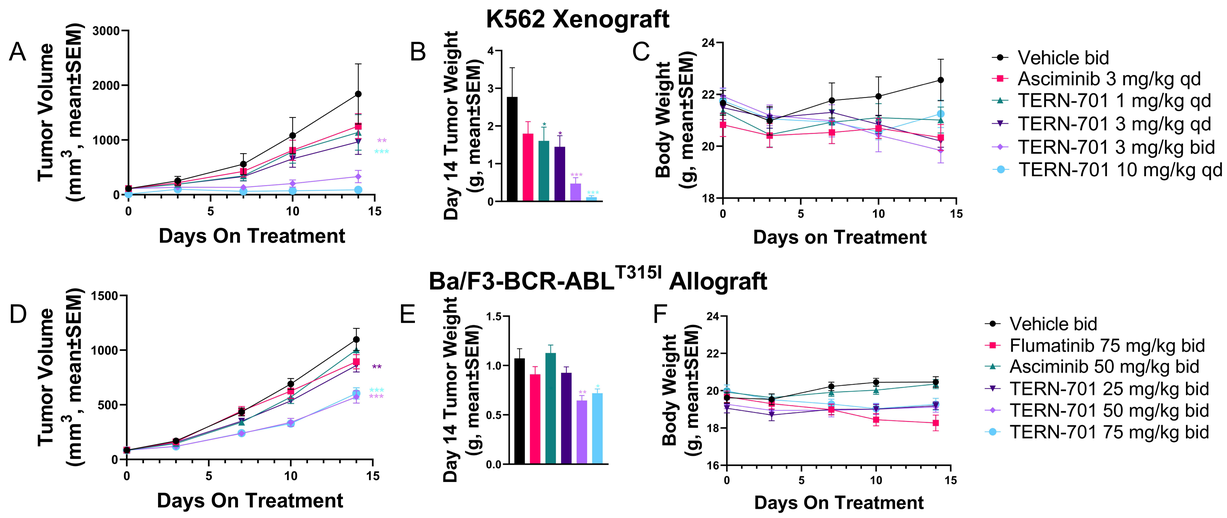
HS-10382, 3 mg/kg, *p.o.*

Time (h)	0	1	2	4	6	8	16	24
Plasma (ng/mL)	0	396	330	230	51	28	BLLOQ	BLLOQ
Tumor (ng/g)	0	183	245	297	179	131	20	21



TERN-701 *in vivo* efficacy

TERN-701 effectively inhibits tumor growth in the K562 and Ba/F3^{T315I} pre-clinical models of CML. A,D) NOD-SCID (K562) and BALB/c nude mice (Ba/F3^{T315I}) were implanted with CML cells, randomized, and administered the indicated TKIs once tumor volumes reached a mean size of 110 mm^3. Tumor volumes were then measured over the 15-day study duration. Flumatinib and asciminib were included as active and allosteric inhibitor comparators, respectively. B,E) Mean tumor weights for each of the treatment groups at the conclusion of the study. C,F) Mean body weights for each cohort did not significantly change throughout the study duration. All error bars represent the SEM.[a]



[a]Statistical analysis was performed using two-way ANOVA (Fisher's LSD multiple comparison test) based on tumor volumes at each time point in each group. *p<0.05, **p<0.01, ***p<0.001

3 CONCLUSIONS

- TERN-701 demonstrated low-nanomolar potency against BCR-ABL1 in biochemical and cell-based assays *in vitro* and showed minimal activity against a panel of 375 kinases, underscoring its selectivity.
- TERN-701 demonstrated time-dependent pharmacodynamic modulation of BCR-ABL1 autophosphorylation and Crkl phosphorylation *in vivo*.
- TERN-701 is an effective and well-tolerated anti-CML agent, outperforming asciminib in the K562 and Ba/F3^{T315I} models at equivalent dosages and dosing schedules (including once-daily dosing).
- TERN-701 is currently in a multi-center Phase 1 dose escalation/expansion trial in the greater China region.

REFERENCES

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2. Quintas-Cardama A, Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood. 2009;113(8):1619-30.
3. Alves R, Goncalves AC, Rutella S, Almeida AM, De Las Rivas J, Trougakos IP, et al. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia-from molecular mechanisms to clinical relevance. Cancers (Basel). 2021;13(19).