Characterization & Efficacy of TERN-701 In Pre-clinical Models of Chronic Myeloid Leukemia

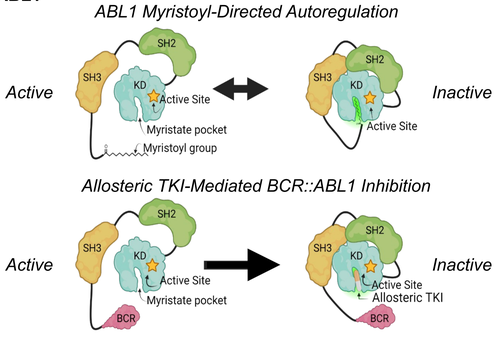
Poster #: CML-592

Ben Parsons, Reema Harish, Kevin Quinn, Christopher Jones, and Jeffrey R. Jasper — Terns Pharmaceuticals, Foster City, CA, United States

INTRODUCTION

Expression of the BCR::ABL1 fusion protein in myeloid cells is a hallmark of chronic myeloid leukemia (CML) (Figure 1).[1,2] Treatment with active site-targeting tyrosine kinase inhibitors has led to improved outcomes in CML, though resistance and intolerance still necessitates therapy switching in up to 50% of those with the disease.[3] TERN-701 is an investigational, next-generation allosteric inhibitor of BCR::ABL1 currently being evaluated for the treatment of CML. It retains potent activity against a wide array of BCR::ABL1 mutations, including the T315I gatekeeper mutation.[4]

Figure 1. Schematic representation of allosteric inhibition of the BCR::ABL1



OBJECTIVES

The objective was to characterize the drug-like properties of TERN-701. We assessed TERN-701's potency against:

- >20 BCR::ABL1 variants
- 450 kinase off-targets
- Panel of >100 cancer cell lines

Finally, the absorption, distribution, metabolism, excretion (ADME), and pharmacokinetics (PK) profile of TERN-701 was characterized.

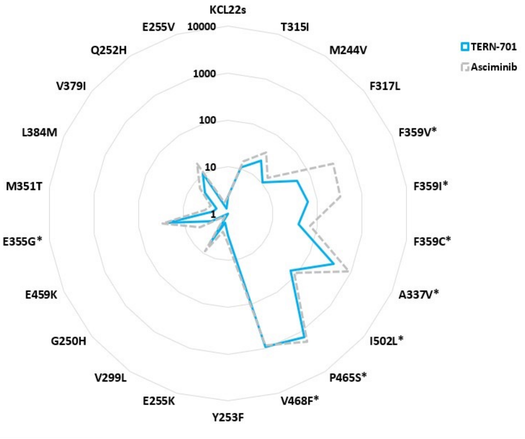
METHODS

- Potency analyses: Murine Ba/F3 cells were stably transfected with a BCR::ABL1 construct containing specified mutations and subsequently exposed to TERN-701 or asciminib for 72 hours. Cell viability was also assessed.
- Selectivity: TERN-701 was screened against more than 450 kinases in both functional and binding assays
- ADME/DMPK properties were evaluated for clearance, solubility, volume of distribution, oral bioavailability, exposures in multiple pre-clinical species, and efflux potential

RESULTS: TERN-701 was Highly Potent

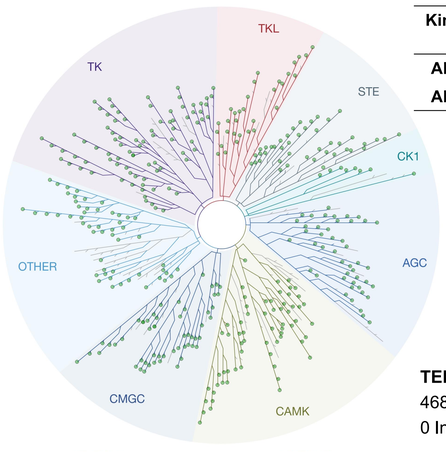
Mutation Cell-Based Potency (IC_{50}, nM)

Figure 2. Cytotoxic potency of TERN-701 and comparator compound asciminib against specified BCR::ABL1 mutations. Asterisks denote mutations known to confer clinically-relevant resistance to allosteric BCR::ABL1 inhibition.



RESULTS: TERN-701 was Highly Selective

Figure 3. TERN-701 did not show significant activity against any of >450 kinases tested at 1 µM, including full-length ABL1 and ABL2.

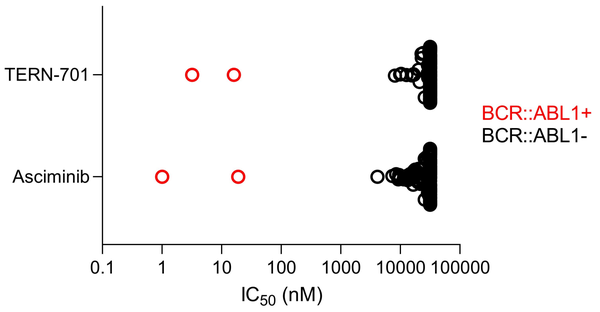


Kinase	% of untreated activity
ABL1	91.6
ABL2	85.5

TERN-701
468 Assays Tested
0 Interactions Mapped

RESULTS: TERN-701 was Highly Selective

Figure 4. TERN-701 exhibited cytotoxicity only against BCR::ABL1+ cell lines in a panel of >100 cell lines.



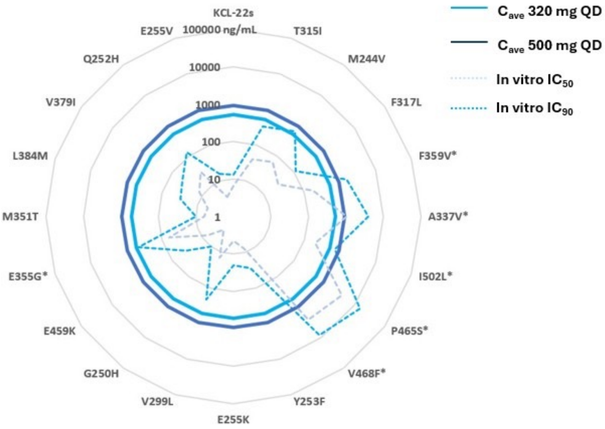
RESULTS: TERN-701 ADME/PK Properties

Table 1. TERN-701 demonstrated low-to-moderate clearance, good oral bioavailability and half life, with good solubility & low efflux potential.

Parameter	Rat	Dog	Predicted Human
CL (mL/min/kg)	27.4±2.65	5.88±1.93	4.7 (2.3-9.3)
Vss (L/kg)	3.23±0.25	2.04±0.205	3.2 (1.6-6.3)
F (%)	72.3±17.2	98.4 ± 12.8	75 (50-100)
T_{max} (hr)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	1.5 (0.8-3)
$T_{1/2,po}$ (hr)	2.49±0.425	8.01±2.63	8 (4-16)

	Test (µM)	Efflux B>A/A>B
Caco2	3	8.22
	10	4.41
	30	2.26

Figure 5. Human Clinical Exposures vs Protein-Corrected Potencies (IC_{90}, ng/mL)



In vitro IC_{90} values corrected for plasma protein binding
*denotes myristoyl mutations or mutations indicated in resistance to allosteric inhibition of BCR::ABL1

DISCUSSION/CONCLUSIONS

TERN-701 demonstrated low-nanomolar potency against many clinically relevant resistance mutations, and was, in most cases, more potent than asciminib. Importantly, when corrected for protein binding, clinical dosages of TERN-701 320 mg and 500 mg QD were predicted to provide coverage over the IC_{90} of most mutations, including T315I and M244V. TERN-701 also demonstrated selectivity that is comparable to asciminib and superior to active-site TKIs[2], with no significant activity against >450 kinases and >100 non-BCR::ABL1-expressing cancer cell lines. These data, when combined with the favorable ADME/PK properties, position TERN-701 as a promising therapeutic option for the treatment of CML. TERN-701 is currently being evaluated in the Phase 1 CARDINAL study (NCT06163430), a global dose escalation/dose expansion clinical trial, in patients with previously treated CML.

REFERENCES

1. Jabbour E, *JAMA*. 2025;333:1618–29.
2. Rinaldi I, et al. *J Blood Med*. 2023;14:261–77.
3. Senapati J, et al. *Blood Cancer J*. 2023;13(1):58.
4. Kitagawa D, et al. *Genes Cells*. 2013;18:110–22.

DISCLOSURES

- B. Parsons, R. Harish, K. Quinn, C. Jones, and J. Jasper are employees and stockholders of Terns Pharmaceuticals