EHA 2025 Congress

12–15 June 2025

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Characterization & Efficacy of TERN-701 in Pre-Clinical Models of Chronic Myeloid Leukemia

Presented by: Timothy Hughes, MD

Ben Parsons, Kevin Quinn, Reema Harish, Christopher Jones, Jeffrey Jasper

Terns Pharmaceuticals, Foster City, CA, USA

Session: s425, Novel Approaches of CML Treatment
13 June 2025, 18:00–18:15 CEST

Disclosures

- TH is an advisory board member for Novartis, Terns, Ascentage, Enliven, and Takeda
  - Research funding: Novartis, Cepheid

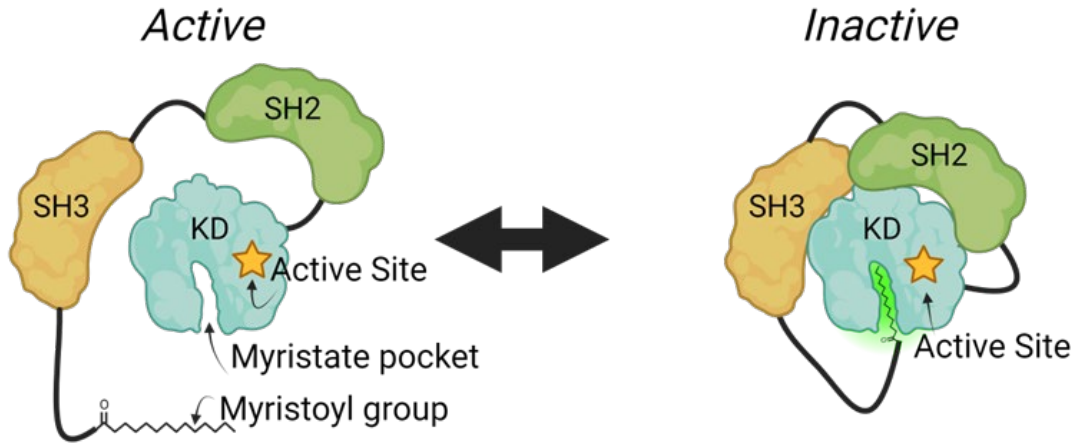
- BP and coauthors are employees of and hold stock and stock options in Terns Pharmaceuticals, Inc.

Background

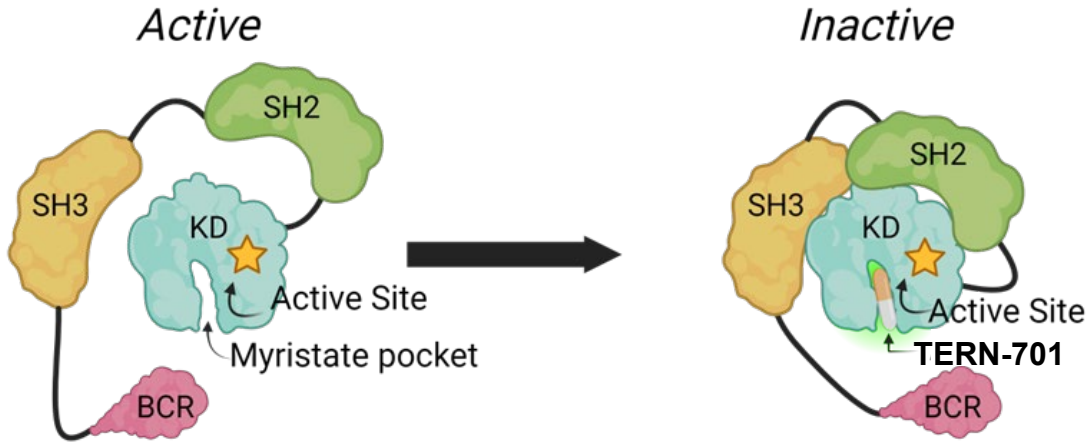
TERN-701 Mechanism of Action

- TERN-701 Specifically Targets the ABL1 Myristoyl Pocket (STAMP) to inhibit BCR::ABL1
- TERN-701 retains strong activity against mutations in the catalytic, P-loop, A-loop, and some SH contact mutations
- Currently in Phase I development for CML

ABL1 Myristoyl–Directed Autoregulation

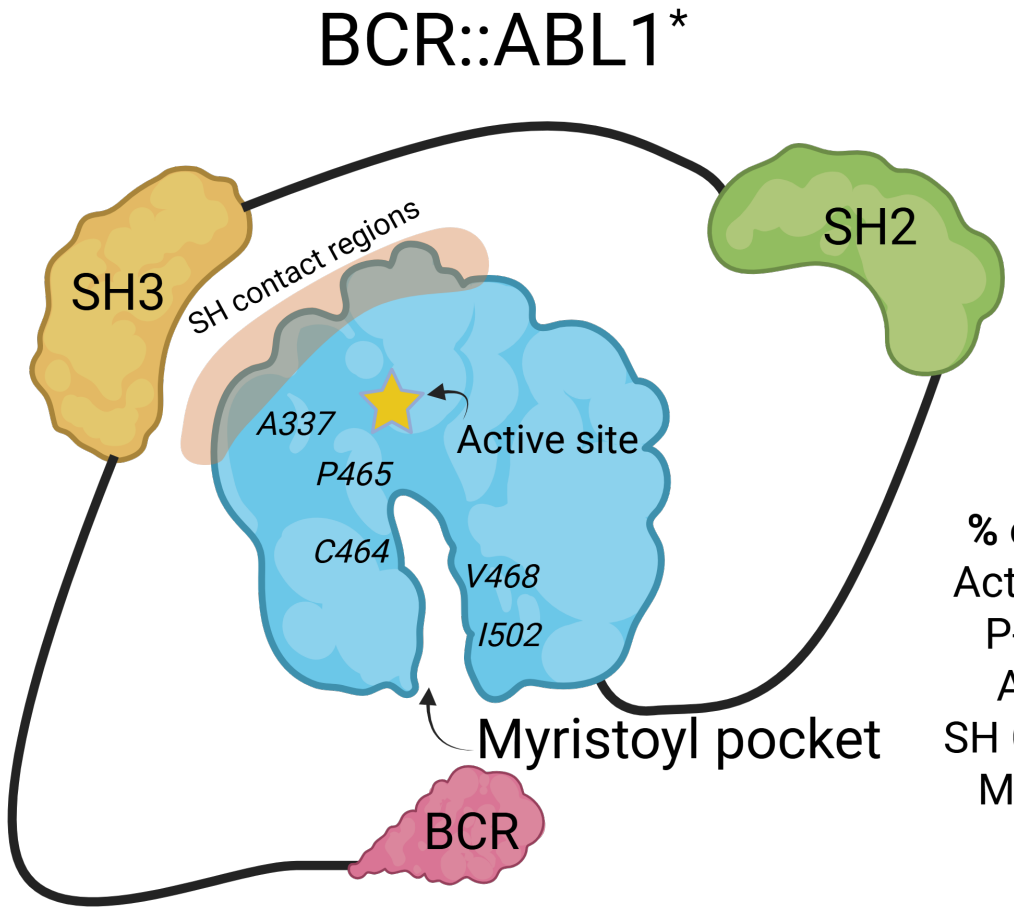


TERN-701–Mediated BCR::ABL1 Inhibition



Background: landscape of BCR::ABL1 mutations

- Although reports vary by cohort, ~50% of CML patients who develop resistance to TKI therapy may have ≥1 underlying BCR::ABL1 resistance mutations[1]
- Majority of mutations are in the active-site (~15%),[2,3] P-loop (~50%)[4], or SH2 contact (~15%)[2] regions
- Myristoyl & allosteric mutations of clinical importance for patients treated with STAMPi



% of Mutations:
Active site: ~15%
P-Loop: ~50%
A-Loop: ~5%
SH Contact: ~15%
Myristoyl: ~5%

*Schematic view; not to scale

Created in https://BioRender.com.

1. Shoukier M, et al. *Curr Oncol Rep*. 2021;23:91.
2. Hawk K, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:10.
3. Perusini M, et al. *Blood*. 2024;144:1.
4. Cang S, et al. *J Hematol Oncol*. 2008;1:15.

Study Objectives

- To investigate the potency of TERN-701 on clinically relevant resistance mutations in the active-site, P-loop, and myristoyl/allosteric regions of the BCR::ABL1 oncoprotein
- To characterize the selectivity of TERN-701 for BCR::ABL1
- To compare pre-clinical activity against exposures observed for humans at multiple dosages

Methods

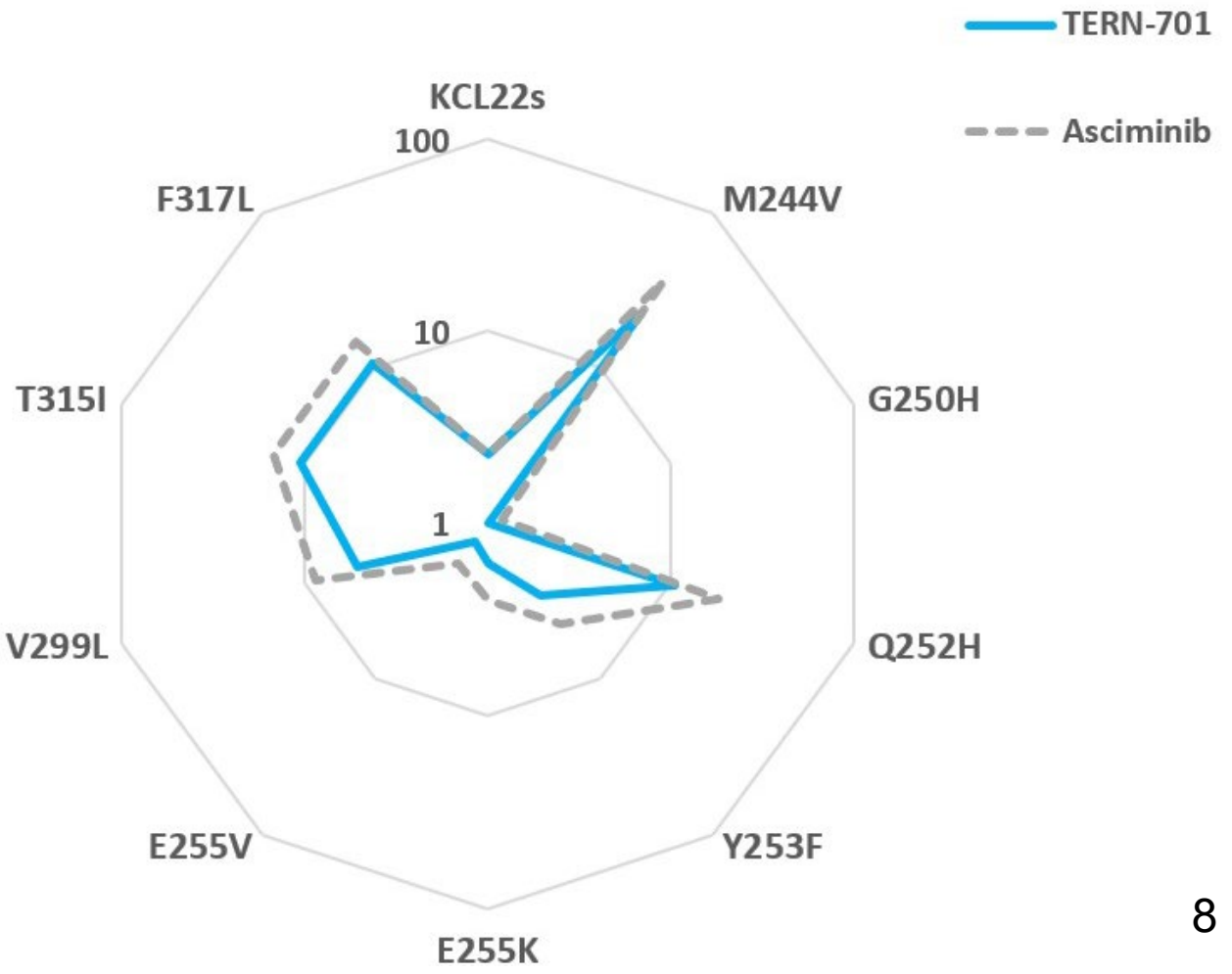
- **Potency analyses:** Murine Ba/F3 cells were:
  - Stably transfected with a BCR::ABL1 construct containing specified mutations
  - Subsequently exposed to TERN-701 or asciminib for 72 hours

- **Selectivity:** TERN-701 was screened against more than 450 kinases in both functional and binding assays

TERN-701 was assessed against clinically relevant BCR::ABL1 mutants

- P-loop mutations highly sensitive to allosteric inhibition
- ATP binding site mutations highly sensitive to allosteric inhibition

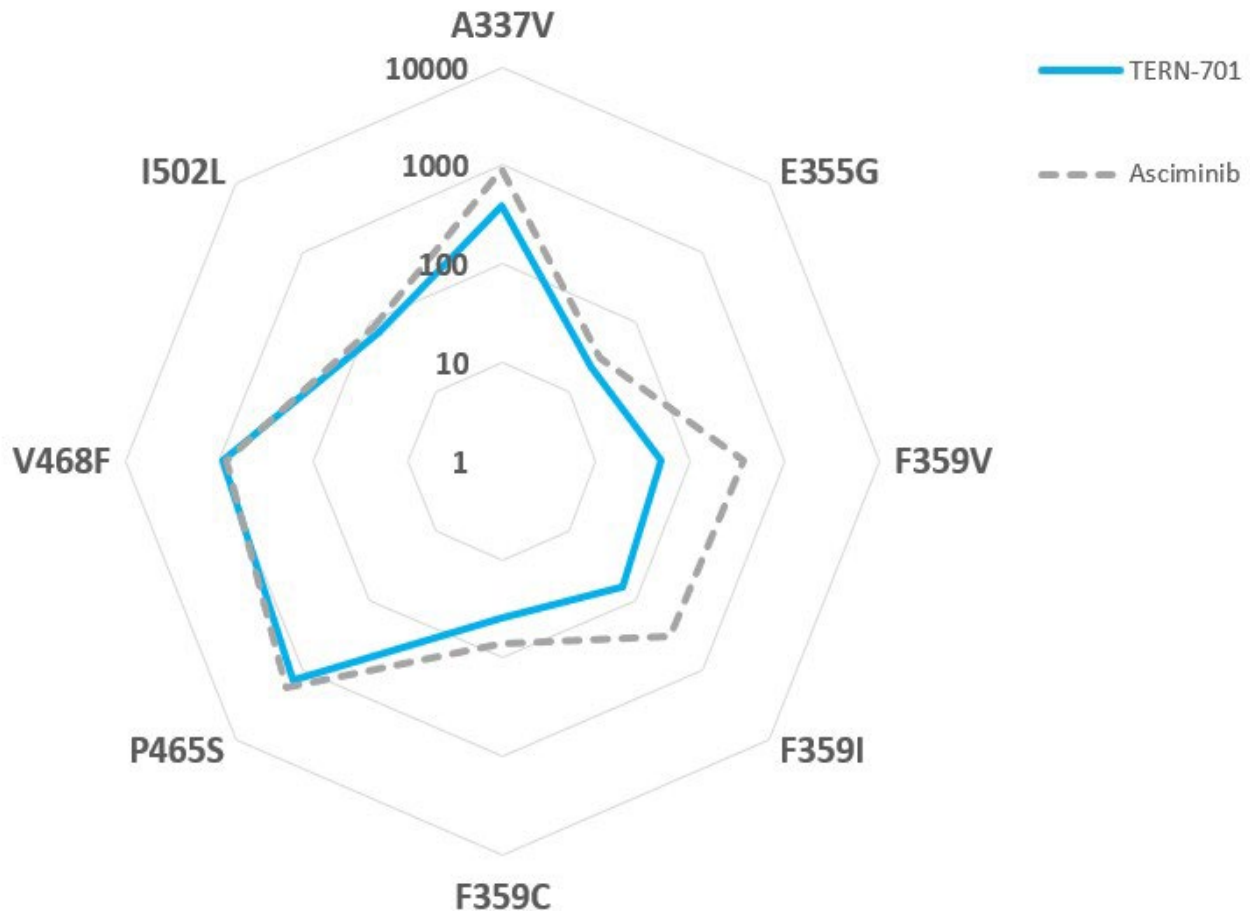
ATP-binding/P-loop Mutation Cell-Based Potency (IC_{50}, nM)



TERN-701 was assessed against mutations in and proximal to the myristoyl pocket

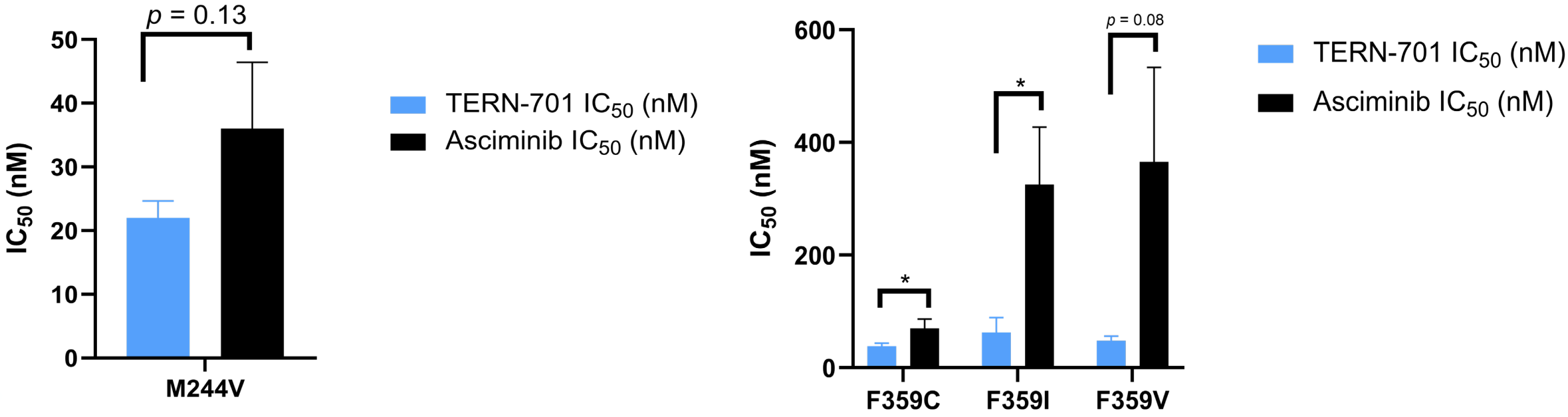
- Myristoyl/allosteric mutations are generally more resistant, consistent with allosteric MOA
  - F359 mutations more sensitive to TERN-701

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



TERN-701 retained activity against select STAMPi resistance mutations *in vitro*

- M244V and F359 mutations more sensitive to TERN-701

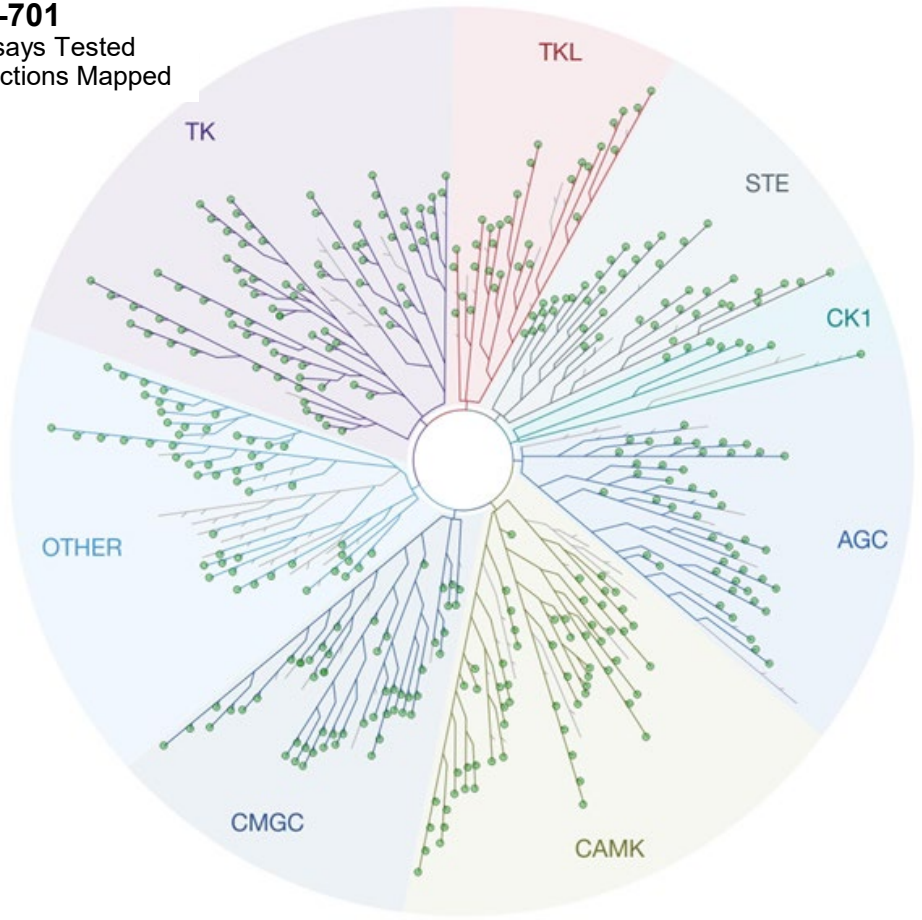


* denotes p<0.05

TERN-701 was highly selective for BCR::ABL1

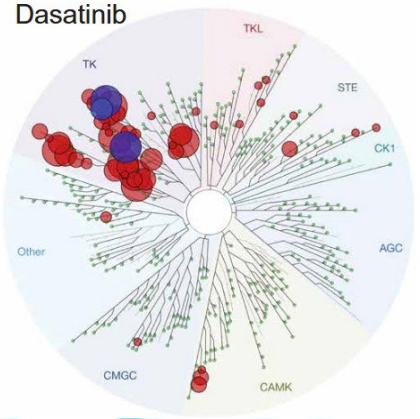
- Exhibited no substantial activity against >450 kinases in functional & binding assays at 1 μM test concentration

TERN-701
468 Assays Tested
0 Interactions Mapped



Each dot represents a single kinase. Kinases significantly modulated appear as red/enlarged

Dasatinib



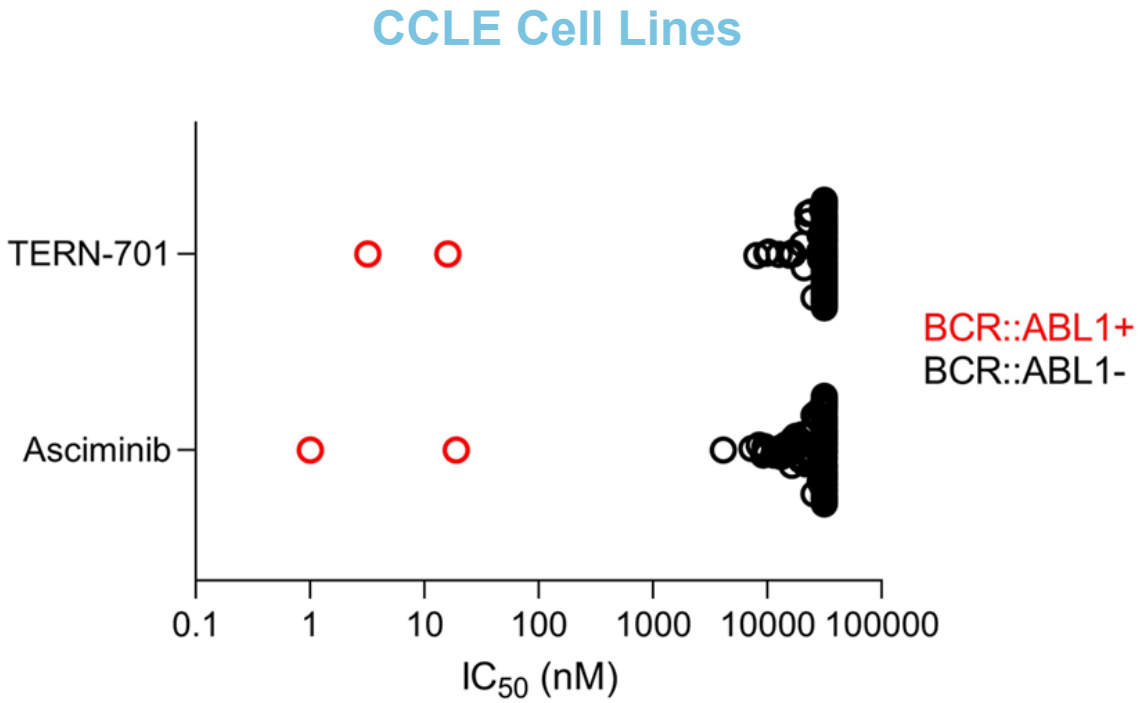
Hu et. al, *Sci Trans Med* 2022

Kinase	% of untreated activity
WT ABL1	**91.6**
WT ABL2	**85.5**

WT = Wild type

TERN-701 was highly selective for BCR::ABL1

- Inactive against a large subset (100+) of BCR::ABL1–negative cell lines



CCLE = Cancer Cell Line Encyclopedia

CARDINAL is an ongoing, global Phase 1 study of TERN-701 in patients with relapsed/refractory chronic phase CML

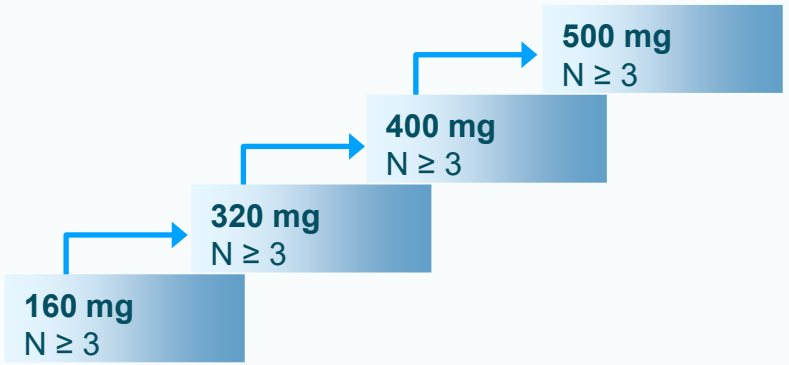
Study Population

Chronic phase **2L+** CML patients w/wo* BCR::ABL1 mutations who have had:

- Treatment failure/suboptimal response OR intolerance to ≥1 TKI
- Prior asciminib allowed

Part 1 Dose Escalation

TERN-701 Once-daily Monotherapy
(N = up to 60 via backfill)

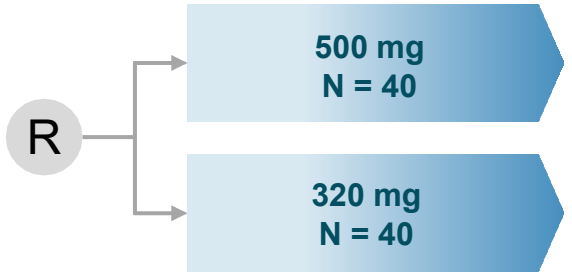


Endpoints For Part 1
- Primary: Safety/tolerability
- Secondary: PK, Efficacy

Part 2 Dose Expansion

TERN-701 Once-daily Monotherapy
(N≈80)

RDE Selection

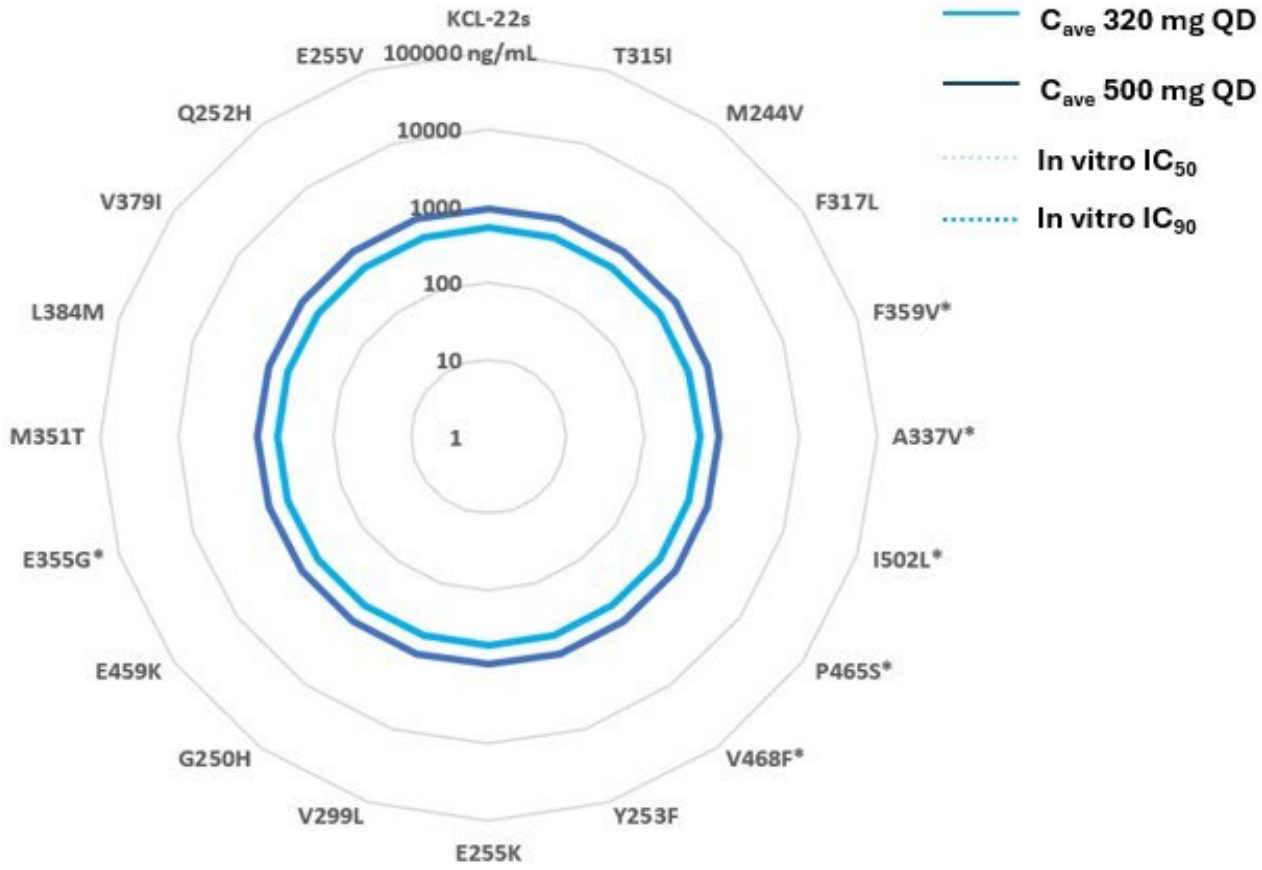


Endpoints For Part 2
- Primary: Efficacy
- Secondary: Safety/tolerability, PK

*ClinicalTrials.gov identifier: NCT06163430
Note: PK: pharmacokinetics; TKI: tyrosine kinase inhibitor

TERN-701 achieved robust target coverage over mutated and non-mutated BCR::ABL1 variants with once-daily dosing

- TERN-701 attains clinical exposures exceeding *in vitro* IC_{90} for multiple CML variants
- Mutations such as M244V, E355G, and I502L may be covered at the 320- and 500-mg QD dosages, with F359V approaching IC_{90} coverage



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

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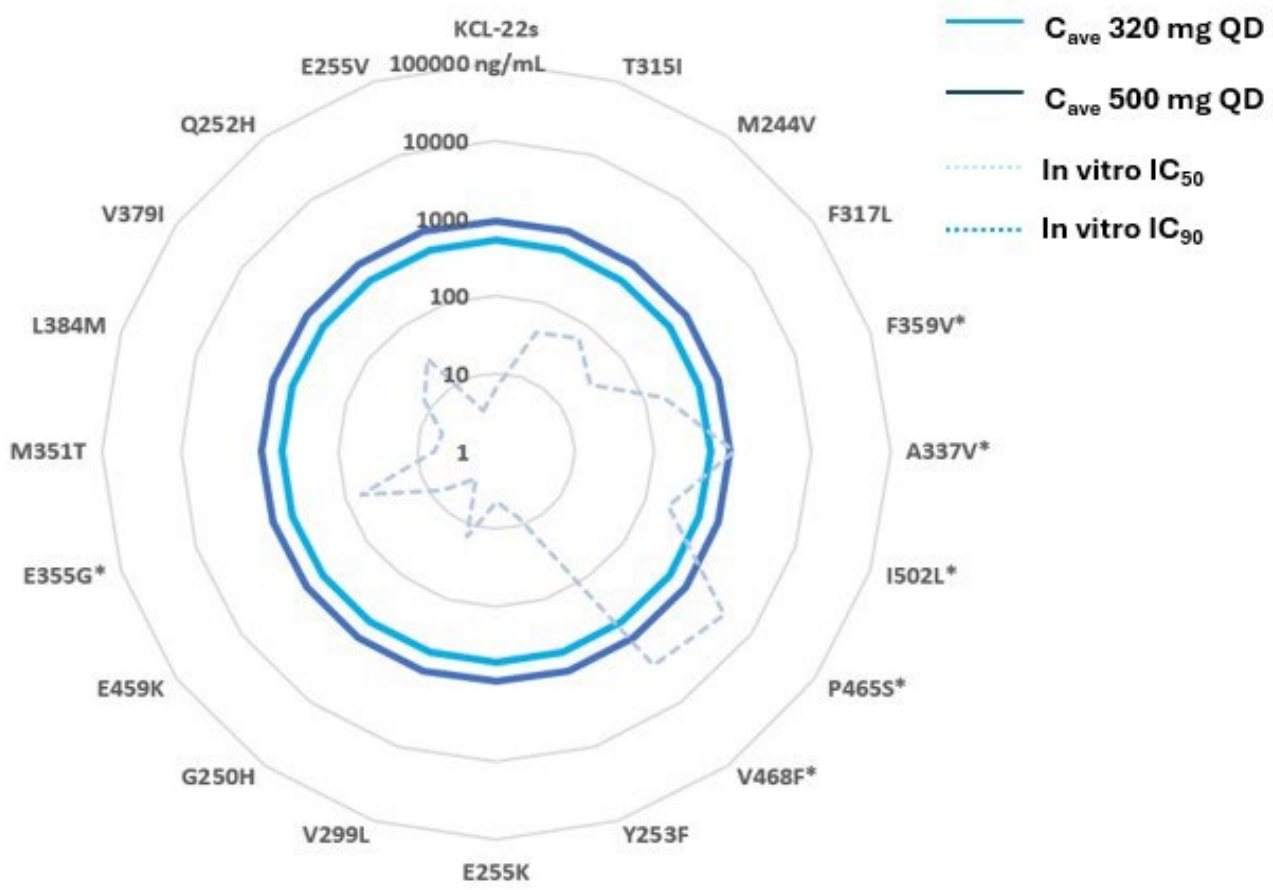

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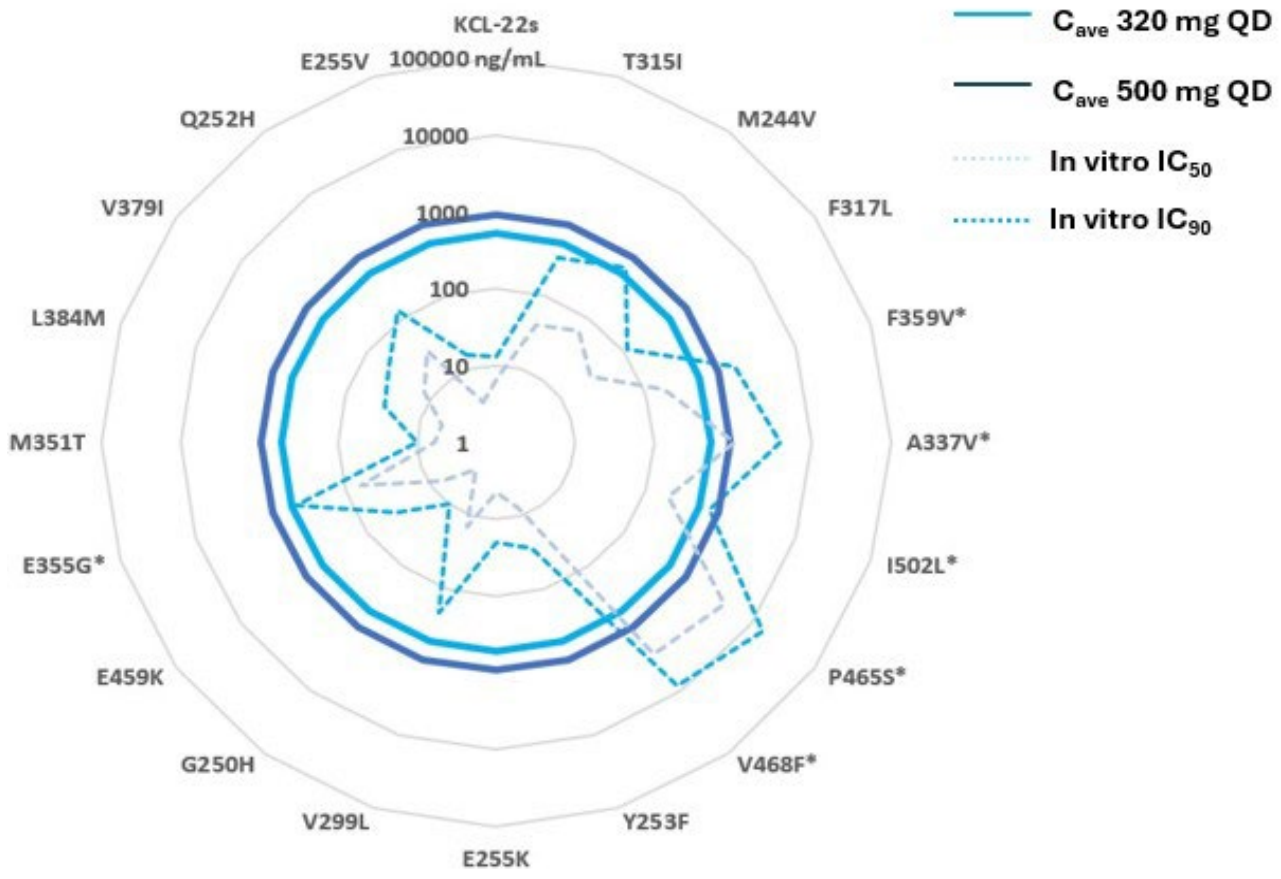

In vitro IC_{90} values corrected for plasma protein binding
* denotes myristoyl mutations or mutations indicated in resistance to allosteric inhibition of BCR::ABL1

Conclusions

- TERN-701 is potent and selective
- Potency values predict coverage of multiple mutations at steady state C_{ave}
- Additional preclinical studies are underway to further characterize TERN-701
- Phase I, dose-escalation/expansion CARDINAL trial (NCT06163430) to evaluate safety and efficacy of TERN-701 is ongoing

Please scan QR code to download a copy of the slides.

Clinical trial registry information for TERN-701 Phase I CARDINAL study