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Preclinical and clinical studies of PEP07, a novel brain-penetrant oral CHK1 inhibitor, on AML and MCL treatments

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Abstract

PEP07 is an orally available and brain-penetrant selective CHK1 inhibitor. CHK1 is involved in the DNA damage response and cell cycle regulation and helps maintain the integrity of the genome during cell division, especially in response to DNA damage or replication stress[1]. Acute myeloid leukemia (AML) is characterized by an impaired DNA damage response (DDR) pathway and elevated CHK1 expression, which correlates with poor patient outcomes[2]. Likewise, mantle cell lymphoma (MCL), a rare and aggressive form of Non-Hodgkin lymphoma, features a chromosomal translocation that leads to cyclin D1 overexpression. Since CHK1 regulates cdk1/cyclin activity, CHK1 inhibitors have been proposed as a novel therapeutic approach in this cancer[3].

In addition to in vitro inhibitory effect on multiple hematology cancer cell lines, PEP07 has been demonstrated as monotherapy to show tumor growth inhibition and tumor regression in the AML and MCL xenograft models, respectively. It also showed enhanced tumor growth inhibition in the cytarabine-resistant AML xenograft model when combined with cytarabine.

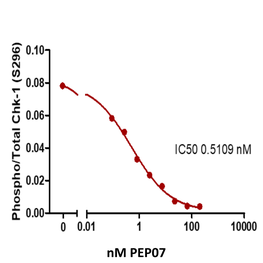
PEP07 is currently being evaluated in clinical studies for both hematologic and solid cancers. PEP07-101 (NCT05659732), a Phase 1b, open-label, multi-center PK/PD and dose-escalating study, employs an accelerated titration design combined with a traditional 3+3 approach assessing PEP07 as monotherapy in patients with relapsed/refractory AML and MCL. With its ability to penetrate the blood-brain barrier (BBB), PEP07 is also being considered for investigating treatment options for brain cancer in clinical settings.

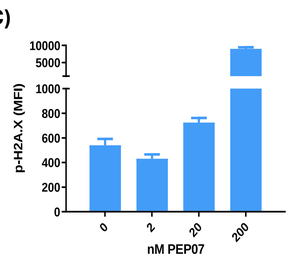
In vitro properties of PEP07

PEP07 is a highly potent and selective CHK1 inhibitor, demonstrating >1000-fold selectivity against Chk2. PEP07 treatment causes inhibition of CHK1 autophosphorylation and activation of the DDR and apoptotic pathways leading to cancer cell death.

(a)

Target	IC50, nM
CHK1	1
Chk2	1630
Flt-3	37
Rsk3	42
Rsk2	83
RET	81
Rsk4	86
Rsk1	125
MAP4K4	242





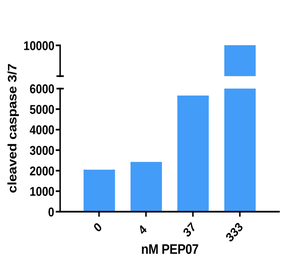


Figure 1. (a) IC50s from ZLYTE FRET-based kinase assay (b) Cellular IC50 as measured by autophosphorylation of pCHK1 S296/total CHK1 in HT29 cells following 18h drug treatment (c) phospho-H2A.X S139 in THP1 AML cell line following 18h drug treatment (d) caspase 3/7 induction in Jeko-1 cell line following 18h drug treatment.

In vitro potency in cell panel and PDC models

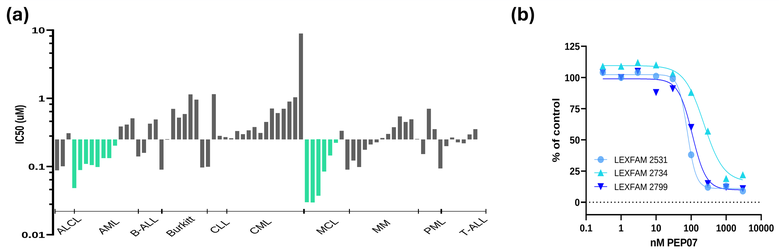


Figure 2. (a) PEP07 demonstrated antiproliferative effects in hematological models, including MCL and AML cell lines, using CellTiter-Glo® viability assays. (b) All three patient-derived AML models showed significant sensitivity to PEP07 treatment.

PEP07 causes regressions in AML and MCL xenografts

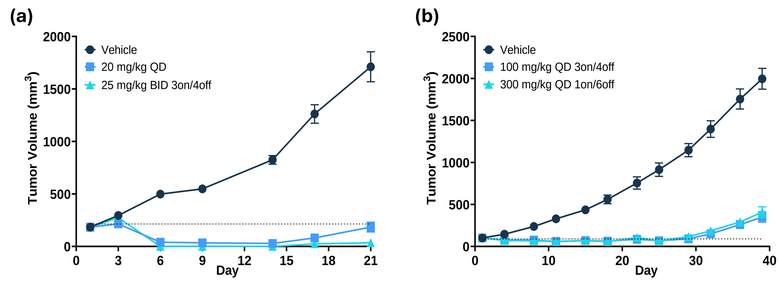


Figure 3. PEP07 has been dosed orally as a single agent using a variety of dosing schedules, where it induces anti-tumor activity and tumor regressions and is well tolerated. (a) Jeko-1 MCL xenograft model. Mice were dosed with PEP07 daily for 21 days at 20 mg/kg or BID 25 mg/kg 3 days on followed by 4 days off. (b) MV-4-11 AML xenograft model. Mice were dosed with PEP07 once a week at 300 mg/kg, or 100 mg/kg for 3 days followed by 4 days off. Dosing was for 4 cycles.

PEP07 combines with Cytarabine and Wee1 inhibitor in AML and MCL xenografts

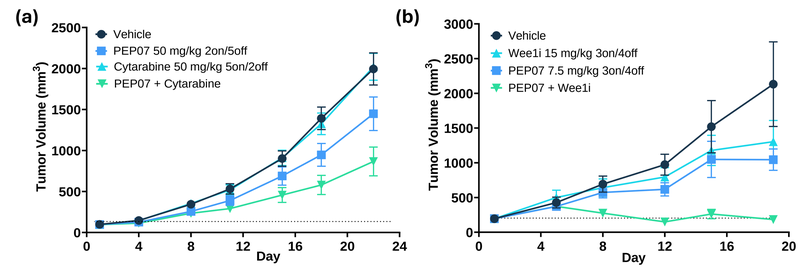


Figure 4. Activity of PEP07 in combination with Cytarabine and Wee1 inhibitor in the THP-1 (Cytarabine-insensitive) and the Jeko-1 xenograft models. (a) THP-1 AML xenograft and (b) Jeko-1 MCL xenograft model, dosed as per the figure legends. PEP07 and Wee1 inhibitor dosed PO and cytarabine dosed IP. Cells were inoculated subcutaneously into the flank of CB17.SCID mice. Once tumors reached a volume of ~ 200 mm^3 mice were randomized into study groups (N= 8- 10). Mice were treated with single agent or both at the doses and schedules indicated.

PEP07 Tumor/Brain penetration

Comparable exposures of PEP07 in the brain and plasma were observed in MV-4-11 AML Model. PEP07 can penetrate the BBB in vivo and significantly accumulates in the tumor.

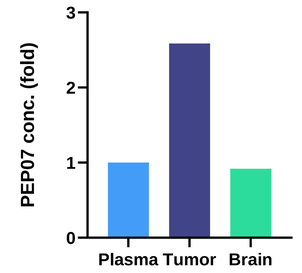


Figure 5. Following a 6-week efficacy experiment, 4 mice were treated with PEP07 and samples collected at 1h after dosing. LC-MS/MS analysis of PEP07 concentration in blood, tumor, and brain samples was conducted.

Clinical Trial of PEP07

The phase 1 clinical study for PEP07 comprises a dose escalation phase in relapsed/refractory (r/r) AML and MCL followed by a dose expansion phase in patients with r/r AML and/or selected tumor types. Patients will receive oral PEP07 treatment until disease progression or un-tolerable adverse event and DLTs will be evaluated during the first treatment cycle. Combination arms will follow to investigate PEP07 combination treatment in patients with r/r AML. Clinical trials are currently underway in both Australia and Taiwan.

Study Design

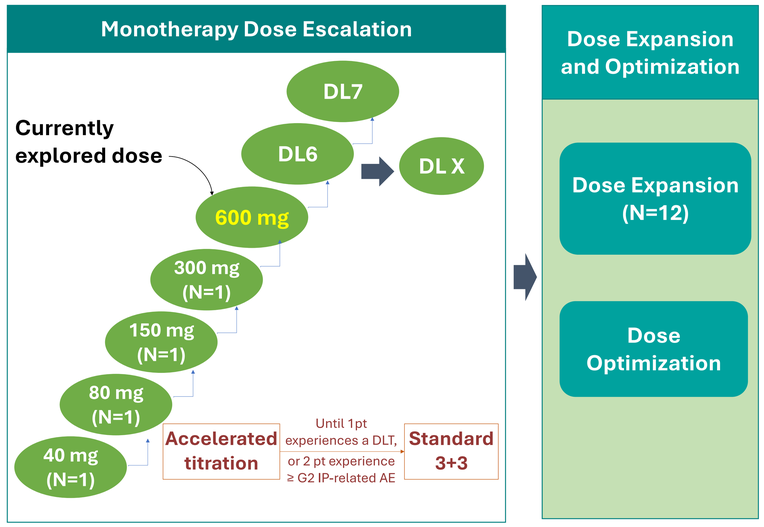


Figure 6. A schematic of the study design and schedule.

Conclusions

- PEP07 is a potent and selective brain-penetrant oral CHK1 inhibitor.
- PEP07 showed strong activity in repressing cancer cell proliferation *in vitro* and tumor growth *in vivo* either by monotherapy or combined with Cytarabine and Wee1 inhibitor in AML and MCL models.
- Clinical trials of PEP07 in AML and MCL are currently underway in both Australia and Taiwan.

References

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