Preclinical Characterization of the First-in-Class MCL-1 Degrader: A Strategy to Bypass Cardiotoxicity Associated with MCL-1 Inhibitors

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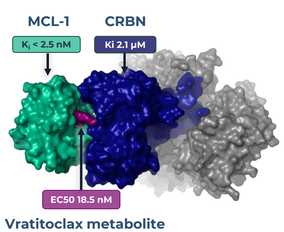
Initial clinical indication: Acute myeloid leukemia (AML)
Modality: Bi-functional degrader, pro-drug
Degradation profile: MCL-1, **Cardiosafe, rapid and irreversible target depletion**
Differentiation from MCL-1 inhibitors:
Degrader eliminates MCL-1 protein, rather than inhibiting its activity - preventing the target accumulation associated with MCL-1 inhibition.
Rapid and irreversible MCL-1 degradation enables potent pharmacological activity following short exposure, without requiring sustained target occupancy
No persistent MCL-1 accumulation and **no cardiotoxicity** observed in human iPSC-derived cardiomyocytes following washout.
Favorable cardiac safety profile in NHPs - no cardiac toxicity observed at exposures above predicted clinically efficacious levels.
Potential to overcome the key limitation of MCL-1 inhibitors: cardiotoxicity associated with MCL-1 stabilization and accumulation

ACUTE MYELOID LEUKEMIA (AML) is the most common acute leukemia in adults and remains an aggressive hematological malignancy associated with poor outcomes. Globally, approximately 145,000 new AML cases and 130,000 deaths were reported in 2021, with the disease burden expected to increase further with population aging. Despite advances in treatment, AML remains challenging to cure, particularly in older and medically unfit patients and in those with relapsed or refractory disease. Current treatment includes intensive induction chemotherapy, targeted agents for selected molecular subtypes, and venetoclax in combination with hypomethylating agents or low-dose cytarabine for patients who are not candidates for intensive chemotherapy.

TARGETED PROTEIN DEGRADATION (TPD) Bi-functional degraders, a class of TPD agents, simultaneously engage an E3 ubiquitin ligase and the target protein, bringing them into proximity to induce ubiquitination and subsequent proteasomal degradation of the target. Here, we report the preclinical characterization and clinical development plan for **vratitoclax**, a first-in-class bi-functional MCL-1 degrader that recruits cereblon (CRBN) to induce **rapid and irreversible degradation of MCL-1** for the treatment of **acute myeloid leukemia (AML).**

MCL-1 degradation induces rapid and irreversible apoptosis by eliminating a key anti-apoptotic protein required for leukemic cell survival. In preclinical studies, vratitoclax demonstrated potent antiproliferative activity across hematological and solid tumor cell models, with rapid MCL-1 degradation and strong cytotoxicity following short exposure. Formation of the CRBN/MCL-1 ternary complex was confirmed using biophysical assays, while MCL-1 degradation was demonstrated by western blotting. **In human iPSC-derived cardiomyocytes, vratitoclax metabolite showed no detectable cardiotoxicity or persistent MCL-1 accumulation after washout, in contrast to MCL-1 inhibitor.** *In vivo*, vratitoclax demonstrated strong antitumor activity in an MV-4-11 AML xenograft model, both as monotherapy and in combination with low-dose venetoclax, here enhanced tumor regression was observed with the combination treatment. **NHP studies further confirmed the favorable cardiac safety profile of vratitoclax at exposures above predicted clinically efficacious levels, alongside a favorable PK/PD profile.**

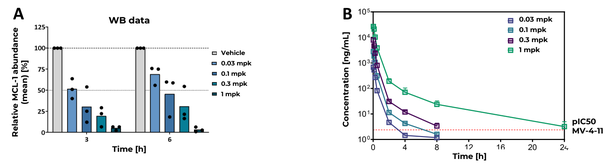


Vratitoclax metabolite

TERNARY COMPLEX

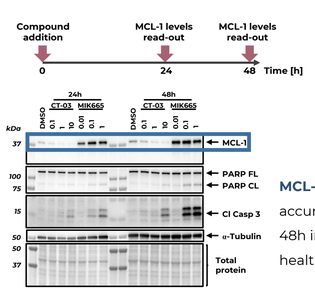
Ternary complex of Vratitoclax metabolite with MCL-1 and Cereblon.
Crystal structures were solved at a high 1.9 Å - 2.3 Å resolution.
Fluorescence polarization (K_i) and TR-FRET (EC_{50}) demonstrate excellent in vitro properties of the molecule.

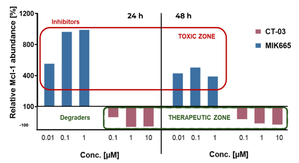
SINGLE-DOSE MCL-1 DEGRADATION IN NHPS



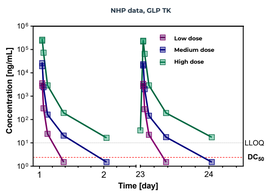
Pharmacodynamics and exposure of Vratitoclax in NHP. A) Western blot and densitometric analysis of PBMCs from male Macaca fascicularis (n=3) following a single IV dose of 1 mg/kg vratitoclax. Almost complete MCL-1 degradation was observed at 3h and 6h post-dose. B) PK profile demonstrating that a 1 mg/kg dose maintains systemic exposure above the MV4-11 pIC_{50} for 24h.

MCL-1 DEGRADERS REMAIN SAFE TO HEALTHY TISSUES





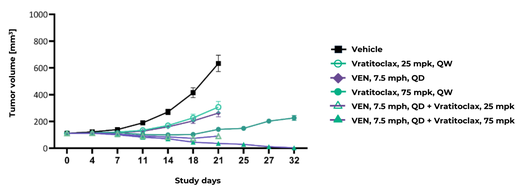
MCL-1 degradation with Vratitoclax metabolite (CT-03) and its accumulation with MIK665 in hiPSC-Cardiomyocytes after 24 and 48h incubation. Inhibitors induce MCL-1 accumulation that is toxic to healthy tissues. Degraders transiently remove MCL-1 in healthy cells.



THERAPEUTIC INDEX AND CARDIAC SAFETY IN NHPs

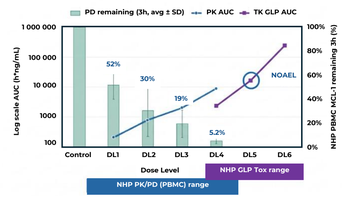
GLP tox studies in NHPs. PK was linear and dose proportional, with no saturated clearance or drug accumulation.
No cardiac pathology was observed at any dose.

HIGH POTENCY OF MCL-1 DEGRADERS IN AN *IN VIVO* AML MODEL



Vratitoclax inhibits tumour growth as monotherapy and induces complete tumour regression in combination with venetoclax in the MV4-11 AML xenograft model. Vratitoclax was administered once weekly (QW) at 25 or 75 mg/kg, while venetoclax (VEN) was administered once daily (QD) at 7.5 mg/kg. Combination treatment resulted in complete tumour regression, demonstrating enhanced antitumour efficacy compared with either monotherapy.

PK/PD-BASED PHASE I STARTING-DOSE SELECTION



Dose-dependent PBMC MCL-1 depletion, PK exposure and GLP toxicology data supported selection of the predicted Phase I starting dose (DL4), at which residual MCL-1 levels were approximately 5.2% of control at 3 h post-dose. GLP studies identified predominantly haematological and lymphoid changes, with recovery or partial recovery, and no cardiac histopathological, ECG or heart-rate effects. A NOAEL was established, and cross-study NHP data suggested a 60–130-fold parent-drug dose margin between doses associated with ~70% PBMC MCL-1 depletion and exposure at the NOAEL.

CLINICAL STUDY DESIGN

The projected Phase 1 BOIN model clinical study at MD Anderson Cancer Center, Huston, USA will enroll patients with **relapsed/refractory acute myeloid leukemia (R/R AML)** and will be conducted in two parts:

Part 1 – Vratitoclax - monotherapy:

Vratitoclax will be evaluated in a dose-escalation phase to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D), followed by dose expansion in selected doses cohorts.

Part 2 – Vratitoclax + venetoclax:

Following identification of the recommended dose (RD) and MTD for venetoclax monotherapy, vratitoclax will be evaluated in combination with venetoclax to determine the combination maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D), followed by dose expansion in selected doses cohorts.

Study endpoints:

Primary: Safety, including determination of MTD and RP2D
Secondary: Efficacy, pharmacokinetics (PK), and pharmacodynamics (PD)
Exploratory: Target engagement and pharmacodynamic biomarkers

CONCLUSIONS & FUTURE DIRECTIONS

Vratitoclax is a first-in-class MCL-1 degrader designed to overcome the cardiotoxicity associated with conventional MCL-1 inhibition through targeted, irreversible protein degradation.
Vratitoclax demonstrates potent and dose-dependent MCL-1 degradation and antitumor activity across *in vitro* and *in vivo* AML models, including tumor regression.
A favourable preclinical safety profile in NHPs, with well-tolerated exposures exceeding those required for therapeutic activity, supports the potential for a clinically relevant therapeutic window.
Vratitoclax is advancing toward clinical evaluation, with a Phase 1 study planned for 2026 in patients with R/R AML, evaluating vratitoclax as monotherapy and in combination with venetoclax.

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