An orally bioavailable, specific PLK1 bifunctional degrader for the treatment of small cell lung cancer and other cancers

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Abstract #4598

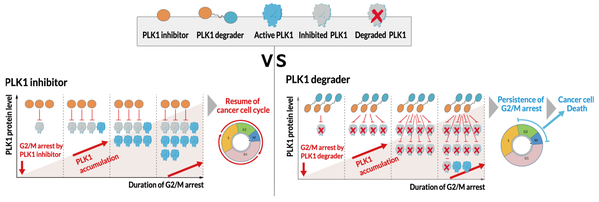
Introduction

PLK1 is a key regulator of the G2/M checkpoint and cell cycle progression, representing a promising therapeutic target across multiple cancer types. However, clinical efficacy of PLK1 inhibitors has been limited largely due to insufficient target suppression at tolerable doses.

PLK1 inhibition induces G2/M arrest but also leads to PLK1 accumulation, necessitating higher doses for sustained effect and contributing to dose-limiting toxicities. In contrast, PLK1 degradation eliminates the target protein via a catalytic mechanism, preventing PLK1 accumulation and enabling sustained G2/M arrest even at lower doses.

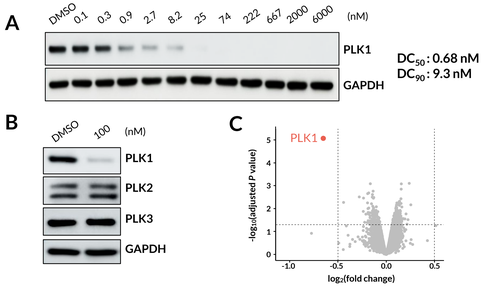
As illustrated below, inhibition results in transient arrest followed by cell cycle recovery, whereas degradation induces persistent arrest and downstream anti-tumor effects. Therefore, PLK1 degradation may overcome the limitations of inhibition by achieving deeper and more durable target suppression without the need for dose escalation.

UP1002 is an orally bioavailable bifunctional degrader that recruits CRBN as an E3 ligase and effectively induces PLK1 degradation, demonstrating potent anti-tumor activity in SCLC and other cancer types.



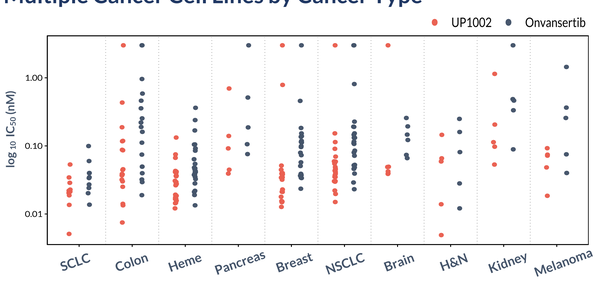
Results

Figure 1: Dose-dependent and Selective PLK1 Degradation of UP1002



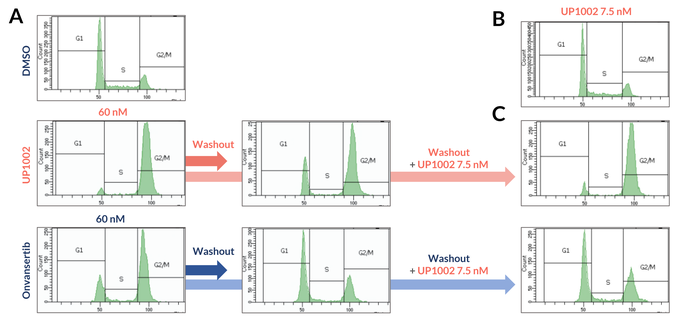
A. Dose-dependent PLK1 degradation in SW1271 cells (48 h).
B. Selective degradation of PLK1 over PLK2/3 in SW1271 cells (30 nM, 72 h).
C. Proteomics confirms selective PLK1 degradation in NCI-H526 cells (50 nM, 4 h).

Figure 2: Anti-proliferative Activity of UP1002 Across Multiple Cancer Cell Lines by Cancer Type



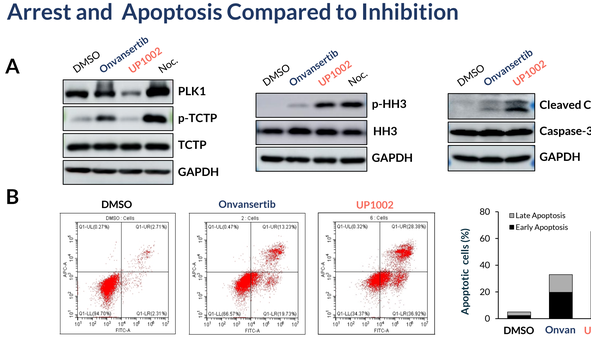
UP1002 demonstrates consistently lower IC_{50} values across cancer types compared to onvansertib (PLK1 inhibitor).

Figure 3: PLK1 Degradation Induced by UP1002 Enables Sustained G2/M Arrest, Unlike Transient Inhibition



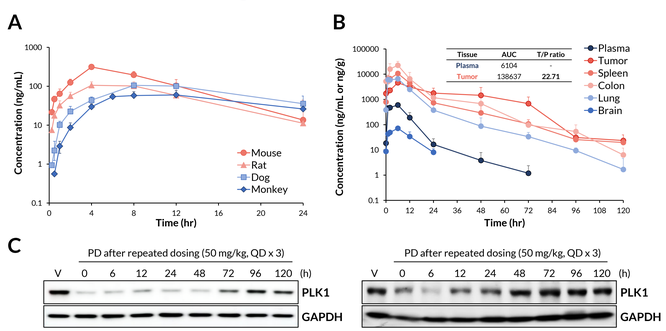
A. Cell-cycle distribution in SW1271 cells following treatment and washout.
B. Low-dose (7.5 nM) treatment does not induce G2/M arrest in naïve cells.
C. Low-dose (7.5 nM) induces G2/M arrest in degrader-pretreated cells, indicating enhanced sensitivity following PLK1 depletion.

Figure 4: PLK1 Degradation Induced by UP1002 Enhances Mitotic Arrest and Apoptosis Compared to Inhibition



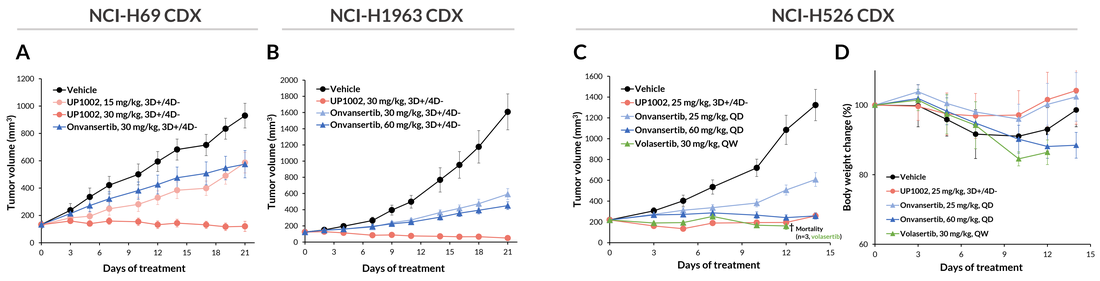
A. PLK1 degradation decreases p-TCTP, increases p-HH3 and cleaved caspase-3 compared to inhibition in SW1271 cells (30 nM).
B. Increased early and late apoptosis with PLK1 degradation versus inhibition.

Figure 5: PK/PD Profile of UP1002 with Tumor-enriched Exposure and Sustained PLK1 Degradation

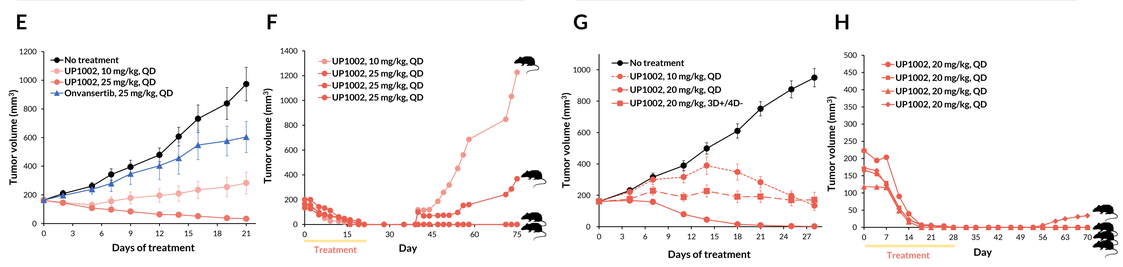


A. Plasma concentration–time profiles following single-dose oral administration (10 mg/kg) across multiple species.
B. Tissue distribution showing higher tumor exposure relative to plasma in the NCI-H69 CDX model after repeated dosing (50 mg/kg, QD x 3; T/P ratio, tumor-to-plasma).
C. Sustained PLK1 degradation in tumor following repeated dosing, with rapid recovery in spleen (50 mg/kg, QD x 3).

Figure 6: In Vivo Efficacy and Durability of UP1002 in SCLC Models

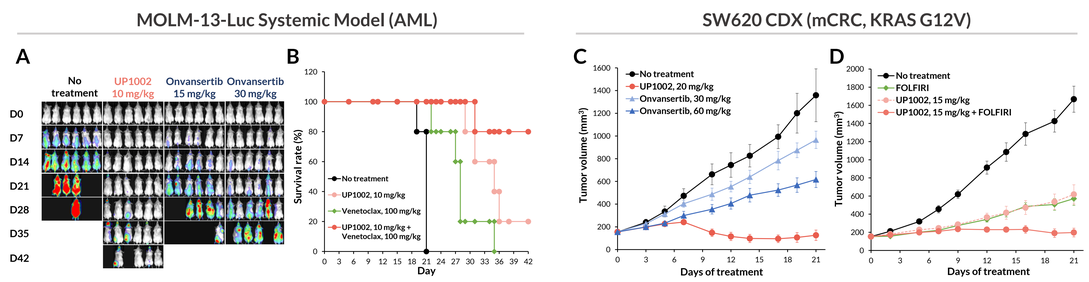


A. Robust anti-tumor activity following oral dosing (3D+/4D-), with the degrader demonstrating superior efficacy than the PLK1 inhibitor and achieving a complete response in one case.
B. Robust anti-tumor activity following oral dosing (3D+/4D-), with the degrader consistently outperforming the PLK1 inhibitor at both equivalent and higher doses.
C. Robust anti-tumor activity relative to PLK1 inhibitors (including IV volasertib).
D. Mortality observed in the volasertib-treated group and body weight reduction at higher doses of onvansertib (60 mg/kg).



E. Robust anti-tumor activity following oral dosing (QD) relative to onvansertib (PLK1 inhibitor).
F. Sustained tumor regression with delayed rebound following treatment discontinuation. Among 4 complete responses (1 at 10 mg/kg; 3 at 25 mg/kg), tumor regrowth was observed at ~3 weeks in two cases, while two cases maintained complete response through the end of study (~8 weeks).
G. Robust anti-tumor activity following oral dosing (QD and 3D+/4D-) in a PDX model.
H. Sustained tumor regression and delayed rebound after treatment discontinuation. Among 4 complete responses (4 at 20 mg/kg, QD) tumor regrowth was observed at ~4 weeks in one case, while three cases maintained complete response through the end of study (~6 weeks).

Figure 7: In Vivo Efficacy and Combination Activity of UP1002 in Additional Cancer Models



A. Robust anti-tumor activity following oral dosing (QD) relative to PLK1 inhibitor.
B. Combination of UP1002 with venetoclax shows synergistic anti-tumor activity under once-daily (QD) dosing, resulting in prolonged survival.
C. Robust anti-tumor activity following oral dosing (QD) relative to PLK1 inhibitor.
D. Combination of UP1002 (QD) with FOLFIRI (QW, IP) shows enhanced anti-tumor activity over monotherapy, consistent with additive effects.

Conclusions

- UP1002 drives potent PLK1 degradation, leading to sustained G2/M arrest and apoptosis in cancer cells, with acceptable tolerability observed in GLP toxicology studies in mouse and beagle dog.
- UP1002 has received U.S FDA IND clearance (Phase 1/2a) in October 2025, with Phase 1b anticipated in 2H 2026.
- The Phase 1b study will evaluate safety, tolerability, PK/PD, and preliminary anti-tumor activity in participants with relapsed/refractory SCLC.