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A Phase 1 study to evaluate the safety, pharmacokinetics, and efficacy of the first-in-class Cyclin A/B RxL inhibitor CID-078, an orally bioavailable, cell-permeable macrocycle

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BACKGROUND

- The cyclin-dependent kinase (CDK)-RB-E2F axis forms the core transcriptional machinery driving cell cycle progression. In many cancers, alterations in *RB1* or other pathway members lead to heightened, oncogenic E2F activity.
- Regulation of E2F activity requires interaction between the cyclin's hydrophobic patch (HP) and the RxL motif found on E2F and other cyclin/CDK substrates and regulators. Blocking this interaction results in hyperactivation of E2F and synthetic lethality in E2F-driven tumors.
- CID-078 is a potent, selective, orally bioavailable, and passively cell-permeable novel macrocycle that blocks HP-RxL binding in both cyclin A2/CDK2-E2F1 and cyclin B1/CDK1-MYT1 to induce cell cycle arrest and apoptotic tumor cell death.
- In preclinical studies, single-agent CID-078 treatment induced tumor regression in multiple E2F-high cancer models including small cell lung cancer (SCLC) and triple negative breast cancer (TNBC). *In vivo* models demonstrated a well-tolerated safety profile and 20% oral bioavailability.

Figure 1. CID-078 is a first-in-class oral macrocycle cyclin A/B-RxL inhibitor that induces G_2/M arrest

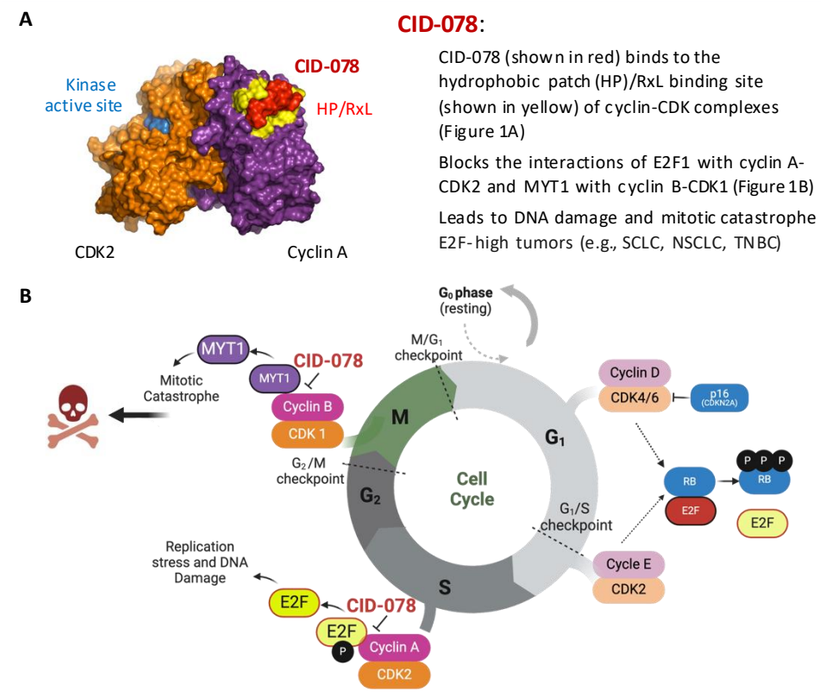


Figure 2. CID-078 activity across a panel of cancer cell lines

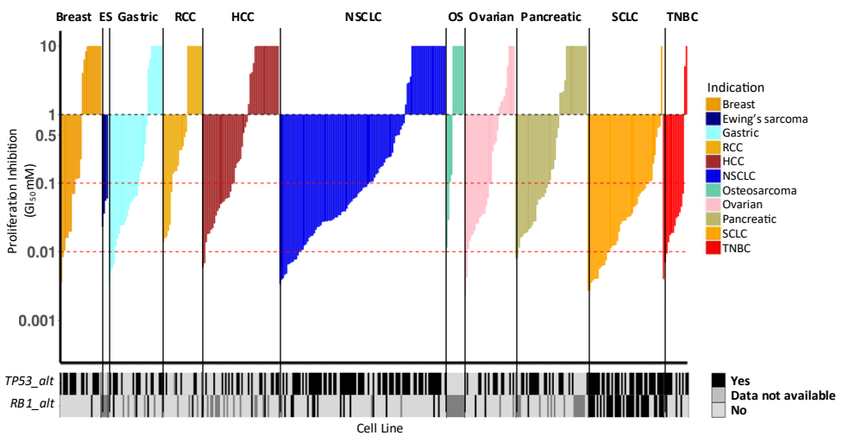


Figure 2. GI_{50} waterfall plots in response to CID-078. CID-078 was profiled for anti-proliferation activity in a broad panel of cell lines representing various solid tumor indications. Cell lines were exposed to CID-078 for 4-8 days depending on length of time required for at least two cell doublings to occur. Cell growth inhibition was determined by Cell Titer Glo assay. *RB1* status was based on genomic alterations (mutation, indel, deletion).

ES, Ewing sarcoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; OS, osteosarcoma; SCLC, small cell lung cancer; TNBC, triple negative breast cancer

Figure 3. *RB1* status is associated with CID-078 sensitivity and high E2F target score

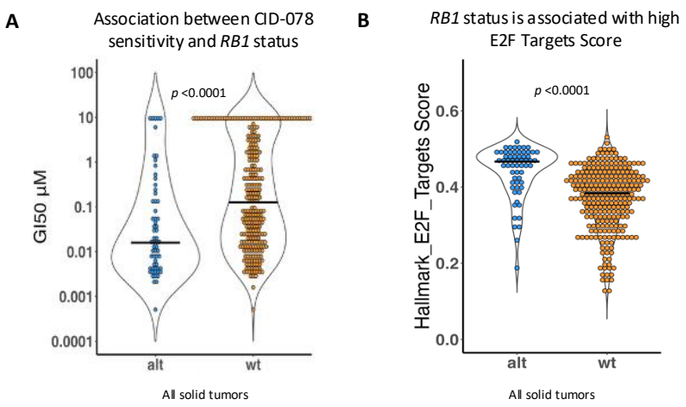
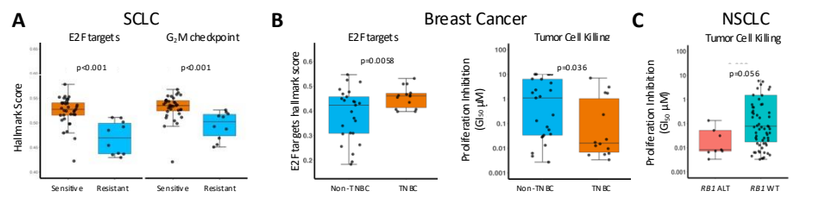


Figure 3. *RB1* status is associated with CID-078 sensitivity. (A) *RB1* status based on genomic alterations (mutation, indel, deletion) is associated with sensitivity to CID-078. **(B)** *RB1* status based on genomic alterations (mutation, indel, deletion) is associated with high E2F Targets Score. E2F Targets Score based on E2F Target Hallmark gene set from MSigDB; E2F high vs low defined by median cut-off across cell line panel (n=327). p-values (shown) calculated by Mann-Whitney test.

Figure 4. E2F targets score and *RB1* alteration is associated with CID-078 sensitivity

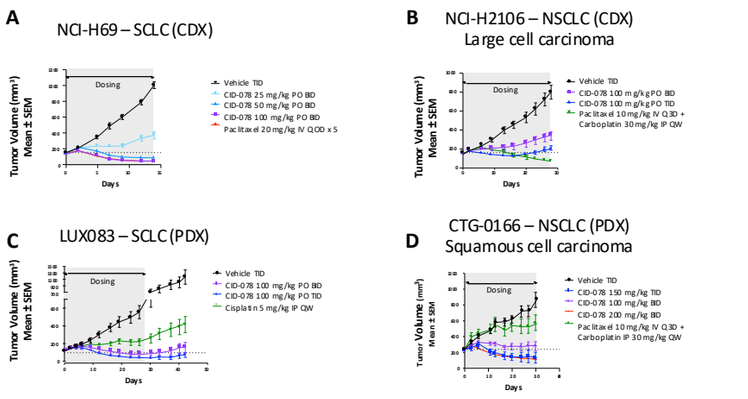


CID-078	*RB1* ALT	*RB1* WT
Sensitive	12 (85.7%)	52 (61.9%)
Resistant	2 (14.3%)	32 (38.1%)

p= 0.12

Figure 4. *In vitro* tumor cell line sensitivity to CID-078. (A) E2F targets and G_2M checkpoint hallmark pathway scores were associated with sensitivity to CID-078 in SCLC cell lines. Sensitivity is defined as GI_{50} < 300 nM. **(B)** Higher E2F targets score and sensitivity to CID-078 is enriched in TNBC. p-values (shown) calculated by Wilcoxon rank sum exact test. **(C)** *RB1* status based on DNA alterations trended with sensitivity to CID-078 in NSCLC cell lines. p-values (shown) calculated by Mann-Whitney test (upper) or Fisher's exact test (lower).

Figure 5. CID-078 shows robust single-agent activity in SCLC and NSCLC CDX and PDX models

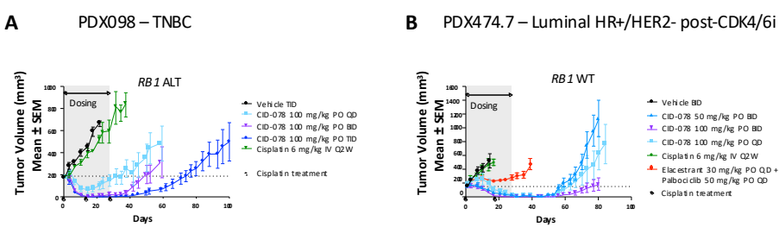


- All models have high E2F targets pathway scores and/or high *E2F1* expression

Figure 5. *In vivo* SCLC and NSCLC xenograft studies. Mice were inoculated SC with $5x10^6$ NCI-H69 **(A)** or $1x10^7$ NCI-H2106 **(B)** CDX cells, or fragments of LUX083 **(C)** or CTG-0166 **(D)** PDX tumors. Treatment was initiated when tumors reached 100-250 mm^3. CID-078 and controls were administered at the doses indicated. All treatment regimens were tolerated as assessed by body weight measurements (not shown). Efficacy results for NCI-H69 represent two studies where controls behaved consistently.

SC, subcutaneous; PO, orally; BID, twice daily; TID, three times daily; QOD, once every two days; Q3D, once every three days; QW, once weekly; SEM, standard error of mean

Figure 6. CID-078 shows robust single-agent activity in a TNBC *RB1* mutant PDX model and a Luminal HR+/HER2- post-CDK4/6 inhibitor PDX model



- Both models have high E2F target pathway scores and high *E2F1* expression

Figure 6. *In vivo* breast cancer xenograft studies. Mice were inoculated SC with fragments of PDX098 **(A)** or PDX474.7 **(B)** PDX tumors. Treatment was initiated when tumors reached 100-300 mm^3. CID-078 and controls were administered at the doses indicated. All treatment regimens were tolerated as assessed by body weight measurements (not shown).

SC, subcutaneous; PO, orally; QD, once daily; BID, twice daily; TID, three times daily; Q2W, once every two weeks; SEM, standard error of mean; PR, partial response; PD, progressive disease

Figure 7. CID-078 shows single-agent activity in CDK-RB-E2F dysregulated tumors

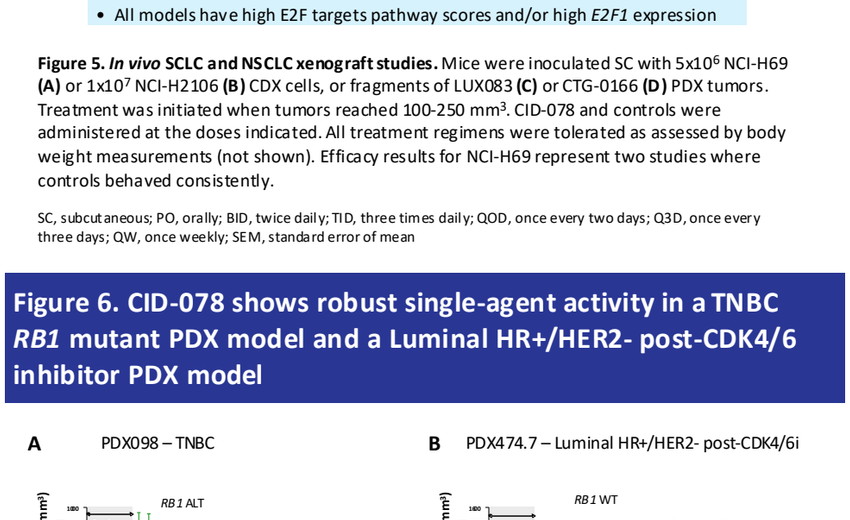


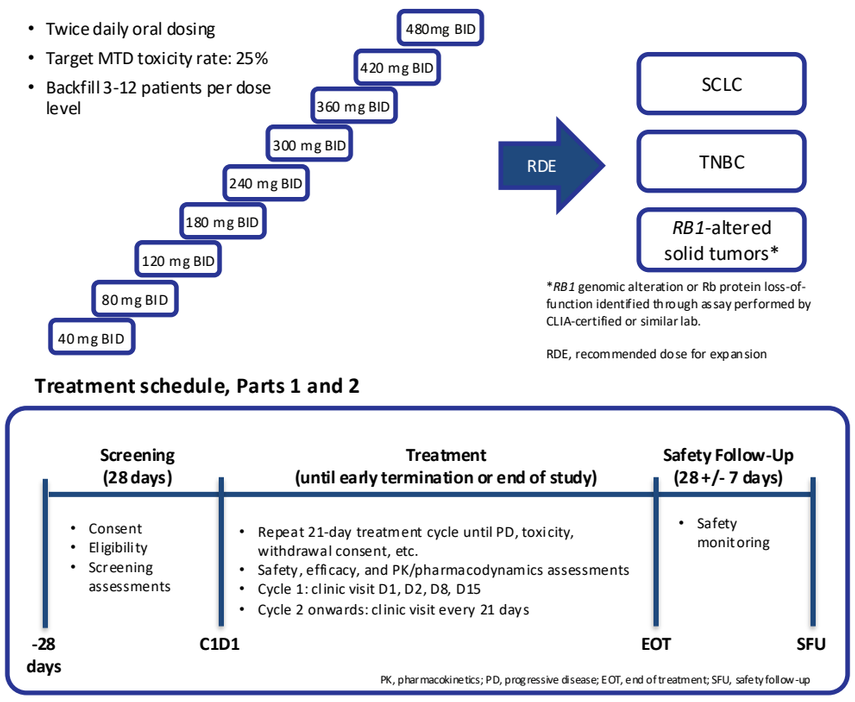
Figure 7. Waterfall plot of *in vivo* efficacy data. (A) Best responses from SCLC, NSCLC, and breast CDX and PDX models is shown along with *RB1* genomic alteration status, *E2F1* gene expression, and G_2M checkpoint and E2F Hallmark Pathway scores. Results for PDX127, PDX124, PDX473B, PDX098, and PDX474.7 are with 100 mg/kg BID dosing of CID-078. Results for CTG-0860, NCI-H1048, PDX600.1, PDX490, PDX479A, NCI-H2106, LUX083, NCI-H23, NCI-H446, and NCI-H69 are with 100 mg/kg TID dosing of CID-078. Results for CTG-0166 are with 200 mg/kg BID dosing of CID-078. N.D., no data. **(B)** *E2F1* gene expression is associated with the maximum tumor growth inhibition observed with any dosing regimen across a panel of PDX/CDX models. *E2F1* high vs low based on median *E2F1* gene expression. p-values (shown) are calculated by the Mann-Whitney test.

METHODS

Study Design

- This is a two-part, Phase I, open label, first-in-human study (CID-AB1-24001 (NCT06577987)) of the cyclin A/B RxL inhibitor CID-078 in patients with advanced solid tumor malignancies.
- Part 1 is a Backfill Bayesian Optimal Interval (BF-BOIN) dose escalation design based on a target MTD rate of 25% (Figure 8). Additional patients may be enrolled to expand previous cohorts to better characterize safety, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy.
- A pilot food effect is planned to evaluate the effect of food on CID-078 PK and safety.
- Part 2 is a dose-expansion phase in which patients will enroll one or more cohorts defined by histologic tumor type or molecular alteration at recommended dose for expansion (RDE).
- Based on preclinical data generated to date, it is expected SCLC, TNBC, and *RB1*-altered tumor cohorts will be expanded.

Figure 8. Study Design



Study Objectives

Part 1 Dose Escalation

Primary objectives
- Evaluate the safety and tolerability of CID-078
- Determine the CID-078 recommended dose(s) for expansion to be examined in Part 2.

Secondary objectives
- Evaluate tumor response/clinical activity of CID-078
- Characterize PK of CID-078
- Evaluate effect of food on the oral PK of CID-078

Part 2 Dose Expansion

Primary objectives
- Evaluate tumor response/clinical activity of CID-078 per RECIST v1.1
- Define provisional Recommended Phase 2 Dose(s) (RP2Ds) of CID-078 to be evaluated in dose optimization

Secondary objectives
- Confirm safety and tolerability of CID-078 at provisional RP2D(s)
- Further characterize PK of CID-078 at provisional RP2D(s)

Key Eligibility Criteria

Inclusion Criteria
- Adults (age ≥ 18 years) with locally advanced or metastatic solid malignancy
- RECIST v1.1 measurable disease (for patients with NSCLC or SCLC and patients with breast cancer in backfill cohort) or evaluable disease
- Eastern Cooperative Oncology Group (ECOG) performance 0-1
- Able to swallow capsules
- Life expectancy ≥ 12 weeks
- Safe laboratory values per protocol
- Archival tumor tissue available or able to undergo fresh biopsy

Exclusion Criteria
- Treatments prior to first dose of study drug of the following: radiotherapy, immunotherapy, or major surgery ≤ 28 days; systemic anti-cancer treatment ≤ 14 days; or targeted therapy ≤ 8 days
- Unresolved Grade ≥ 2 toxicity from previous anti-cancer treatment, except chronic/stable toxicities
- Suspected brain metastases or spinal cord compression, unless treated and stable
- Malabsorption or conditions that may interfere with absorption of product
- History of another primary malignancy ≤ 2 years prior to starting study drug, except for adequately treated cancer
- Uncontrolled intercurrent illness as detailed in protocol or social situations limiting compliance with study requirements

Study Assessments

Efficacy/PK assessments
- CT, PET/CT, or MRI every 6 weeks until disease progression or early termination
- RECIST v1.1 response assessment by investigator
- PK sample collection

Safety Assessments

Safety evaluations will include results of physical examinations, vital sign measurements, ECGs, adverse events and serious adverse events, concomitant medications, ECOG performance status, and local safety laboratory tests as detailed in study protocol.

Exploratory assessments

Blood and tumor samples will be collected for biomarker analysis potentially including but not limited to evaluation of ctDNA, target engagement, biological effects of the treatment, and potential predictors of response to therapy.

Summary and Study Status

- CID-078 is a potent, selective, orally bioavailable novel macrocycle that induces apoptosis in E2F-driven tumors.
- Cohorts 1 (40mg BID) through 6 (300mg BID) appear safe and well tolerated and enrollment to cohort 7 (360mg BID) commenced in May 2025.

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