#3125: A PHASE 1, EVALUATING THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF FADRACICLIB, AN ORAL CDK2/9 INHIBITOR, IN SUBJECTS WITH ADVANCED SOLID TUMORS AND LYMPHOMA

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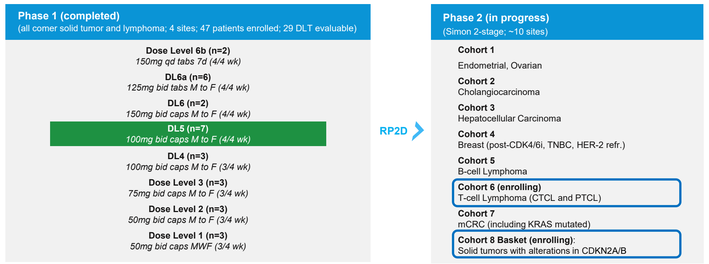
BACKGROUND

- Fadraciclib (formerly CYC065) is a highly selective inhibitor of CDK2 (IC_{50}= 5 nM) and CDK9 (IC_{50}= 26 nM) causing mitotic catastrophe and apoptotic death of cancer cells at sub-micromolar concentrations.
- In an earlier Phase 1 study of intravenous (IV) fadraciclib, confirmed CR has been achieved in a heavily pretreated endometrial cancer patient with CDNK2A, CDKN2B and MTAP loss.
- Oral fadraciclib is highly bioavailable allowing flexibility of dosing and schedule.

METHOD

- This is an open-label, multicenter phase 1/2 study in adult subjects with advanced solid tumors and lymphoma (NCT04983810/CYC065-101).
- Phase 1 explores both schedule and dose of oral fadraciclib monotherapy in 28-day cycles to identify maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). Once RP2D is established, phase 2 will enroll up to 40 subjects in seven tumor specific cohorts and a basket cohort (tumor agnostic but molecularly driven), utilizing a Simon two-stage optimal design to evaluate clinical activity (**Figure 1**).
- Primary objectives
  - Phase 1: To determine MTD and/or RP2D
  - Phase 2: To evaluate preliminary efficacy of fadraciclib as measured by overall response rate (ORR)
- Secondary objectives
  - Phase 1: To assess safety and tolerability, PK, and ORR
  - Phase 2: To assess safety and tolerability; to evaluate disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS)
- Exploratory objectives: To investigate clinical pharmacodynamics (PD) and pharmacogenomics (PGx) of fadraciclib

Figure 1: CYC065-101 Study Design



RESULTS

Table 1: Patient Disposition

	50mg BID MWF Wk 1-3	50mg BID M-F Wk 1-3	75mg BID M-F Wk 1-3	100mg BID M-F Wk 1-3	100mg BID M-F Wk 1-4	150mg BID M-F Wk 1-4	125mg BID M-F Wk 1-4	150mg QD Wk 1-4	Total
Patients who received at least one dose of treatment, n (%)	3 (100)	4 (100)	3 (100)	3 (100)	9 (100)	2 (100)	13 (100)	10 (100)	47 (100)
DLT evaluable Patients [a], n	3	3	3	3	7	2	6	2	29
Patients who discontinued the treatment, n (%)	3 (100)	4 (100)	3 (100)	3 (100)	9 (100)	2 (100)	13 (100)	9 (90.0)	46 (97.8)
Primary reason for treatment discontinuation, n (%)									
Withdrawal of consent	0	0	0	0	1 (11.1)	0 (0)	5 (38.5)	3 (30.0)	9 (19.1)
Adverse event	1 (33.3)	1 (25.0)	0	0	1 (11.1)	0 (0)	1 (7.7)	2 (20.0)	6 (12.8)
Disease progression	2 (66.7)	3 (75.0)	2 (66.7)	3 (100)	6 (66.7)	1 (50.0)	6 (46.2)	4 (40.0)	27 (57.4)
Pregnancy	0	0	0	0	0	0	0	0	0
Investigator decision	0	0	0	0	1 (11.1)	0	0	0	1 (2.1)
Sponsor decision	0	0	0	0	0	0	0	0	0
Other	0	0	1 (33.3)	0	0	1 (50.0)	1 (7.7)	0	3 (6.4)
All-Treated Subjects Set [b]	3	4	3	3	9	2	13	10	47
DLT-Evaluable Patients Set	3	3	3	3	7	2	6	2	29
Full Analysis Set [c]	3	4	3	3	6	1	9	6	35

[a] DLT-Evaluable Patients: All patients who received at least 80% of the doses and completed all safety evaluations required for initiating Cycle 2. [b] All-Treated Subjects Set: All enrolled patients who received at least 1 dose of study drug. [c] Full Analysis Set: All treated patient's subset with measurable disease at baseline and have at least one post-baseline disease assessment.

Table 2: Patient Demographics and Baseline Characteristics – All Treated Subjects (N=47)

(A)	Total (N=47)
Age (years)	
Mean (SD)	58.6 (12.60)
Median	60.0
Min, Max	36, 81
Sex, n (%)	
Female	30 (63.8)
Male	17 (36.2)
ECOG performance status, n (%)	
0	9 (19.1)
1	38 (80.9)
Number of Prior Anti-cancer therapy, n (%)	
Mean (SD)	5.43 (3.67)
Median	4.0
Min, Max	1; 17

(B)	Total (N=47)
Primary tumor site, n (%)	
Appendix	3
BTC	4
Breast	9
CRC	6
CUP	1
Gyn	7
H&N	3
HCC	2
Lung	3
Melanoma	1
Pancreatic	2
Prostate	2
Testis	1
T cell lymphoma	3

CONCLUSIONS

- Common adverse events observed across all cohorts include nausea, vomiting and fatigue, while hyperglycemia and platelet decrease were observed primarily at higher dosing cohorts. Dose reductions occurred frequently above the RP2D. DLTs at doses above RP2D were nausea and hyperglycemia.
- Pharmacokinetics were dose-proportional and exceeded the preclinical efficacy target for both CDK2 and CDK9. Pharmacodynamics evaluated in peripheral blood showed suppression of CDKN2A/B by 4 hours post treatment in most patients who received 100 mg bid or higher.
- Clinical benefit was observed across all cohorts in a number of tumor types, including endometrial, NSCLC, ovarian, pancreatic and T-cell lymphoma.
- Based on the totality of safety, pharmacokinetic, pharmacodynamic and preliminary efficacy data, the **RP2D of 100 mg bid p.o. Monday to Friday** was selected.
- Enrollment of Phase 2 is in progress.

SAFETY

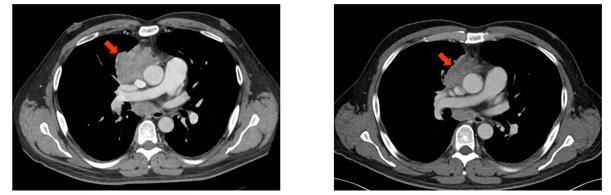
- The most common treatment related adverse events reported were nausea (66.0%), vomiting (46.8%), diarrhea (31.9%) fatigue (25.5%), and hyperglycemia (21.3%).
- Fadraciclib was well tolerated with good compliance between dose levels 1-5. A total of 4 DLT were reported at dose levels 6 (nausea, n=1; and hyperglycemia, n=1) and 6a (hyperglycemia, n=2).
- A total of 25 drug-related SAEs were reported in 8 patients with most common being hyperglycemia (n=4), platelet count decrease (n=3), and accidental overdose (n=3). There were no drug-related SAEs in dose level 5 (100 mg bid) the RP2D.
- Three deaths were reported on treatment. None were related to treatment.

EFFICACY

- A total of 35 patients were evaluable for efficacy (34 with measurable target lesions at baseline) as of April 29th, 2024. Tumor evaluations were conducted at baseline, end of Cycle 1 and then every 2 cycles. Response criteria of RECIST 1.1 were used for solid tumors (n=32), Lugano (n=2) and mSWAT (n=1) for PTCL and CTCL patients enrolled in the study.
- Two PRs were reported at dose levels 2 and 5 in patients with T-cell lymphomas.
- A heavily pretreated NSCLC patient with CDKN2A/B loss achieved 22% reduction in tumor burden at 4 weeks (**Figure 2**).
- Clinical benefit was reported in 7 patients (2 each with T-Cell lymphomas and endometrial cancer, and 1 with NSCLC, ovarian, and pancreatic respectively.)

EFFICACY (cont.)

Figure 2: CT Scan of a patient with squamous NSCLC (DL6a)

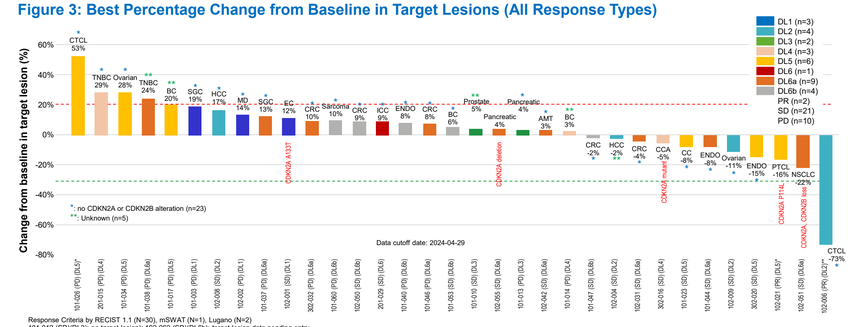


Baseline scan 7-SEP-23 *Cycle 1 scan 9-OCT-23*

*50y old male with sqNSCLC and **CDKN2A and CDKN2B** loss. Prior treatments included carboplatin and paclitaxel (from November 2022 to April 2023) followed by docetaxel and atezolizumab (May 2023) with progression. Patient's first scan after four weeks of therapy showed **SD (-22%)***

Images kindly provided by the principal investigator.

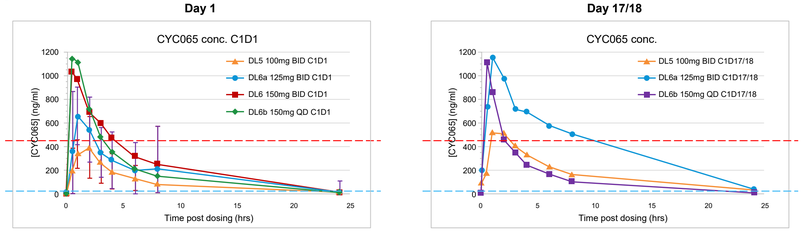
Figure 3: Best Percentage Change from Baseline in Target Lesions (All Response Types)



Response Criteria by RECIST 1.1 (N=30), mSWAT (N=1), Lugano (N=2)
101-012 (SD)(DL3): no target lesion); 102-062 (SD)(DL6b): target lesion data pending entry
AMT = Appendix; BC: Breast; CC = Cervix; CCA = Cholangiocarcinoma; CRC = Colon and Rectum; CTCL = Cutaneous T cell Lymphoma; EC = Uterus; ICC = Intrahepatic bile ducts; ENDO = Endometrial; HCC = Hapatocellular Carcinoma; MD = Mandible; SGC = Salivary gland; TNBC = Triple-Negative Breast Cancer

PHARMACOKINETICS

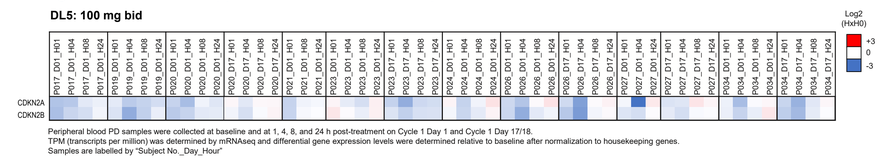
Figure 4: Plasma Concentration of CYC065 post Treatment



PK samples were collected in patients on Cycle 1 Day 1 and Cycle 1 Day 17/18. Dose proportional PK with CDK2 and 9 coverage at higher dose levels.

PHARMACODYNAMICS

Figure 5: Fadraciclib Suppressed CDKN2A/B Transcription in Patients



Peripheral blood PD samples were collected at baseline and at 1, 4, 8, and 24 h post-treatment on Cycle 1 Day 1 and Cycle 1 Day 17/18.
TPM (transcripts per million) was determined by mRNAseq and differential gene expression levels were determined relative to baseline after normalization to housekeeping genes.
Samples are labelled by "Subject No._Day_Hour"