# A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety, Pharmacokinetics, and Efficacy of Fadraciclib (CYC065), an Oral CDK2/9 Inhibitor, in Subjects with Advanced Solid Tumors and Lymphoma


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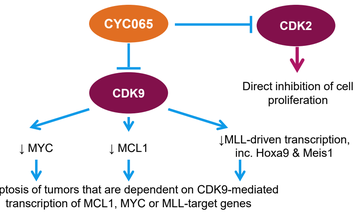
## INTRODUCTION

- Fadraciclib (CYC065) is a highly selective, orally- and intravenously- available, 2nd generation amino-purine inhibitor of CDK2 and CDK9, being developed as a therapeutic agent for cancers dependent on MCL1 and MYC through the inhibition of CDK9, and for cancers associated with CCNE1 amplification, a known resistance factor for trastuzumab and CDK4/6 inhibitors, through the inhibition of CDK2 (**Figure 1**).
- In an earlier Phase 1 study of IV fadraciclib, confirmed CR has been achieved in a subject with MCL1-amplified endometrial cancer.
- Oral fadraciclib is highly bioavailable allowing flexibility of dosing and schedule.

### Figure 1: Fadraciclib Proposed Mechanism of Action




## METHODS

- This is an on-going 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 12 to 40 subjects in seven specific tumor-type groups and a basket cohort, utilizing a Simon two-stage optimal design to evaluate clinical activity (**Figure 2**).
- Safety, pharmacokinetics (PK) and efficacy will be investigated for all subjects
- Primary objectives
  - Dose Escalation: To determine MTD and/or RP2D
  - Proof of Concept: To evaluate preliminary efficacy of fadraciclib as measured by overall response rate (ORR)
- Secondary objectives
  - Dose Escalation: To assess safety and tolerability, PK, and ORR
  - Proof of Concept: 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 2: CYC065-101 Study Design

**Phase 1**
(3+3 design; 4 sites)

Dose Level 7
200mg bid daily M to F, wk 1-4

**Dose Level 6**
**150mg bid daily M to F, wk 1-4**

✓ Dose Level 5
100mg bid daily M to F, wk 1-4

✓ Dose Level 4
100mg bid daily M to F, wk 1-3

✓ Dose Level 3
75mg bid daily M to F, wk 1-3

✓ Dose Level 2
50mg bid daily M to F, wk 1-3

✓ Dose Level 1
50mg bid daily MWF, wk 1-3

**Phase 2**
(Simon 2-stage; ~10 sites)

**Cohort 1**
Endometrial, Ovarian

**Cohort 2**
Cholangiocarcinoma

**Cohort 3**
Hepatocellular Carcinoma

**Cohort 4**
Breast (post-CDK4/6i, TNBC, HER-2 refr.)

**Cohort 5**
B-cell Lymphoma

**Cohort 6**
T-cell Lymphoma (CTCL and PTCL)

**Cohort 7**
mCRC (including KRAS mutated)

**Cohort 8 Basket**: tumors suspected to have related MoA (expand if responses)

## RESULTS

### Table 1: Patient Demographics and Baseline Characteristics

| | 50mg BID MWF Wk 1-3 (N=3) | 50mg BID M-F Wk 1-3 (N=4) | 75mg BID M-F Wk 1-3 (N=3) | 100mg BID M-F Wk 1-3 (N=3) | 100mg BID M-F Wk 1-4 (N=8) | Total (N=21) |
|---|---|---|---|---|---|---|
| Age (Years) | | | | | | |
| Mean (SD) | 53.0 (8.5) | 69.0 (3.7) | 68.7 (5.2) | 53.3 (5.8) | 63.6 (7.9) | 62.4 (9.2) |
| Median | 58 | 72 | 76 | 47 | 65 | 54 |
| Min; Max | 41; 60 | 65; 75 | 64; 76 | 47; 61 | 51; 73 | 41; 76 |
| Sex, n (%) | | | | | | |
| Female | 2 (66.7) | 2 (50.0) | 1 (33.3) | 3 (100.0) | 5 (62.5) | 13 (61.9) |
| Male | 1 (33.3) | 2 (50.0) | 2 (66.7) | 0 (0.0) | 3 (37.5) | 8 (38.1) |
| ECOG performance status, n (%) | | | | | | |
| 0 | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 4 (50.0) | 5 (23.8) |
| 1 | 3 (100.0) | 3 (75.0) | 3 (100.0) | 3 (100.0) | 4 (50.0) | 16 (76.2) |
| Primary tumor site, n (%) | | | | | | |
| Breast | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 2 (25.0) | 4 (19.0) |
| Cervix | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 1 (4.8) |
| Gallbladder & Extrahepatic bile ducts | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (33.3) | 2 (25.0) | 3 (14.3) |
| Liver | 0 (0.0) | 2 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (9.5) |
| Ovary | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.8) |
| Pancreas | 0 (0.0) | 0 (0.0) | 1 (33.3) | 0 (0.0) | 0 (0.0) | 1 (4.8) |
| Prostate | 0 (0.0) | 0 (0.0) | 2 (66.7) | 0 (0.0) | 0 (0.0) | 2 (9.5) |
| Salivary glands | 1 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.8) |
| Skin | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 2 (9.5) |
| Other | 2 (66.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (25.0) | 4 (19.0) |
| Cancer stage at initial diagnosis, n (%) | | | | | | |
| Stage I | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Stage II | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (33.3) | 1 (12.5) | 3 (14.3) |
| Stage III | 1 (33.3) | 1 (25.0) | 0 (0.0) | 2 (66.7) | 3 (37.5) | 7 (33.3) |
| Stage IV | 2 (66.7) | 2 (50.0) | 3 (100.0) | 0 (0.0) | 2 (25.0) | 9 (42.9) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (25.0) | 2 (9.5) |

### Table 2: 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 | Total |
|---|---|---|---|---|---|---|
| Screened patients, n [a] | 3 | 6 | 4 | 3 | 11 | 27 |
| Screen failures, n | 0 | 2 | 1 | 0 | 3 | 6 |
| Patients who received at least one dose of treatment, n (%) | 3 (100) | 4 (100) | 3 (100) | 3 (100) | 8 (100) | 21 (100) |
| Patients who discontinued the treatment, n (%) | 3 (100) | 4 (100) | 3 (100) | 3 (100) | 5 (62.5) | 18 (81.8) |
| Primary reason for treatment discontinuation, n (%) | | | | | | |
| Withdrawal of consent | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (12.5) | 1 |
| Adverse event | 1 (33.3) | 2 (50.0) | 1 (33.3) | 0 (0) | 1 (12.5) | 5 |
| Disease progression | 1 (33.3) | 2 (50.0) | 0 (0) | 3 (100) | 3 (37.5) | 9 |
| Pregnancy | 0 (0) | 0 (0) | 2 (66.7) | 0 (0) | 0 (0) | 2 |
| Investigator decision | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 |
| Sponsor decision | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 |
| Other | 1 (33.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 |
| Missing | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 |
| All-Treated Subjects Set [b] | 3 (100) | 4 (100) | 3 (100) | 3 (100) | 8 (100) | 21 |
| DLT-Evaluable Patients Set [c] | 3 (100) | 3 (75.0) | 3 (100) | 3 (100) | 6 (75.0) | 18 |
| Full Analysis Set [d] | 3 (100) | 4 (100) | 3 (100) | 3 (100) | 5 (67.5) | 18 |

[a] All patients who signed the informed consent form or those who had their legally authorized representative sign for them.
[b] All-Treated Subjects Set: All enrolled patients who received at least 1 dose of study drug.
[c] DLT-Evaluable Patients Set: All patients who received at least 80% of the doses and completed all safety evaluations required for initiating Cycle 2.
[d] Full Analysis Set: All treated patient's subset with at least one post-baseline disease assessment.

## SAFETY

### Table 3: Overview of Treatment-Emergent Adverse Events – All Treated Subjects Set, All Cycles, Related and Unrelated

| | 50mg BID MWF Wk 1-3 (N=3) | 50mg BID M-F Wk 1-3 (N=4) | 75mg BID M-F Wk 1-3 (N=3) | 100mg BID M-F Wk 1-3 (N=3) | 100mg BID M-F Wk 1-4 (N=8) | Total (N=21) |
|---|---|---|---|---|---|---|
| Any TEAE | 3 (100) | 4 (100) | 3 (100) | 3 (100) | 6 (75.0) | 19 (90.4) |
| Grade ≥3 | 2 (66.7) | 4 (100) | 2 (66.7) | 1 (33.3) | 3 (37.5) | 12 (57.1) |
| Leading to dose reduction | 0 | 0 | 0 | 0 | 0 | 0 |
| Leading to temporary interruption of study drug | 0 | 3 (75.0) | 1 (33.3) | 0 | 1 (12.5) | 5 (23.8) |
| Leading to permanent discontinuation of study drug | 1 (33.3) | 1 (25.0) | 2 (66.7) | 0 | 1 (12.5) | 5 (23.8) |
| Leading to death | 0 | 1 (25.0) | 0 | 0 | 0 | 1 (4.7) |
| Any related TEAE | 2 (66.7) | 4 (100) | 3 (100) | 3 (100) | 6 (75.0) | 18 (85.7) |
| Grade ≥3 | 2 (66.7) | 4 (100) | 0 | 0 | 1 (12.5) | 7 (33.3) |
| Any serious TEAE, Unrelated | 2 (66.7) | 2 (50.0) | 2 (66.7) | 1 (33.3) | 1 (12.5) | 8 (38.1) |
| Grade ≥3 | 1 (33.3) | 2 (50.0) | 2 (66.7) | 1 (33.3) | 0 | 6 (28.6) |
| Any related serious TEAE | 0 | 0 | 0 | 0 | 0 | 0 |

TEAE: Treatment-Emergent Adverse Event
Note 1: TEAE is defined as any adverse event with the onset date on or after the first dose of study treatment, or any adverse event with an onset date before the first dose of study treatment but which has worsened in severity after the first dose of study treatment until 30 days after the last dose of study treatment.
Note 2: Percentage are calculated using the number of patients included in All-Treated Subjects Set as denominator.

## EFFICACY

### Table 4: Best Tumor Response per Investigator Review – Full Analysis Set

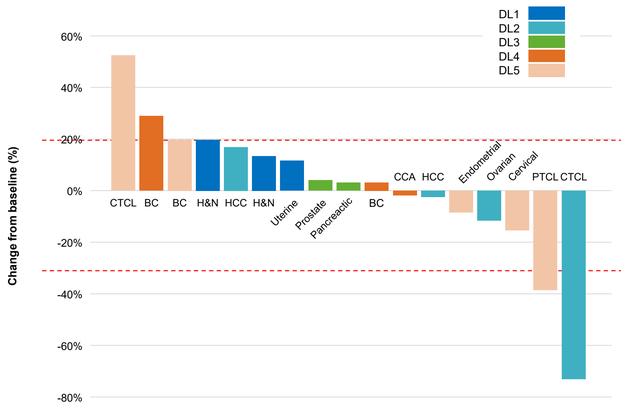
| | Dose level 1 50 mg BID MWF week 1 to 3 (N=3) | Dose level 2 50 mg BID MWF week 1 to 3 (N=4) | Dose level 3 75 mg BID MWF week 1 to 3 (N=3) | Dose level 4 100 mg BID MWF week 1 to 3 (N=3) | Dose level 5 100 mg BID MWF week 1 to 4 (N=6)* |
|---|---|---|---|---|---|
| Best overall response (BOR), n (%) | | | | | |
| Complete response | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Partial response | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 1 (16.7) |
| Stable disease | 2 (66.7) | 3 (75.0) | 3 (100.0) | 1 (33.3) | 2 (33.3) |
| Progressive disease | 1 (33.3) | 0 (0.0) | 0 (0.0) | 2 (66.7) | 2 (33.3) |
| Not evaluable | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

*One subject response pending
Best Tumor Response was done per Investigator Review. Full Analysis Set: All treated patient's subset with at least one post-baseline disease assessment.
Response criteria: RECIST 1.1 (N=15), mSWAT (N=1), Lugano (N=2)

### Table 5: Tumor Response per Cancer Type

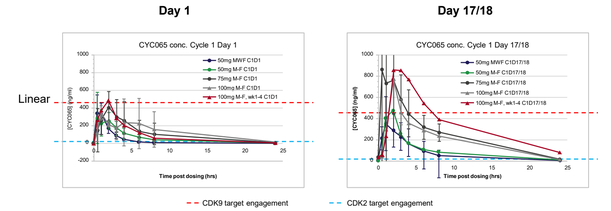
| Best Overall Response | n/N (%) |
|---|---|
| Complete response | 0/18 (0.0) |
| Partial response | 2/18 (11.1) |
| Stable disease | 11/18 (61.1) |
| Progressive disease | 5/18 (27.8) |
| Disease control (SD+PR) per cancer type | 13/18 (72.2) |
| **Gyn (Endometrial, ovarian, cervical)** | **4/4 (100)** |
| **Cholangiocarcinoma, BTC** | **1/1 (100)** |
| **Hepatocellular carcinoma** | **2/2 (100)** |
| Breast cancer | 0/3 (0) |
| **T-cell lymphoma** | **2/3 (66.7)** |
| **Prostate cancer** | **2/2 (100)** |
| Head and Neck | 1/2 (50) |
| **Pancreatic cancer** | **1/1 (100)** |

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




## PHARMACOKINETICS

### Figure 4: Plasma Concentration of CYC065 post Fadraciclib Treatment in DL 1-5 Patients

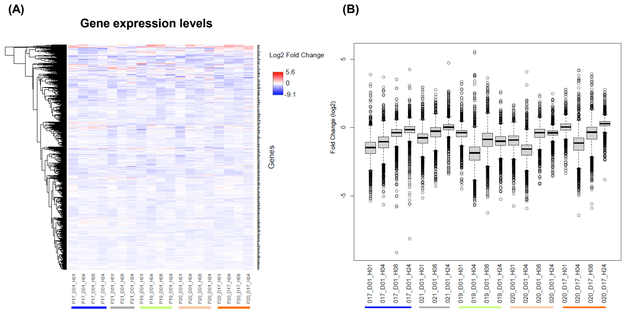



PK samples were collected in patients on Cycle 1 Day 1 and Cycle 1 Day 17/18.

Plasma concentrations of CYC065 (mean ± SD) of dose levels 1-5 were presented.

## PHARMACODYNAMICS

### Figure 5: DL5 Fadraciclib Pharmacodynamic Response in Whole Blood by RNAseq




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 was determined by mRNAseq and differential gene expression levels were determined relative to baseline after normalisation to housekeeping genes.

(A) For 1h or 4h timepoints the average fold change (across samples) in gene expression is ≥2 for 3347 protein-coding genes, whose differential gene expression is illustrated by heatmap. (B) Boxplot of the distribution of gene expression fold changes across samples for these genes. Mean is horizontal line, 2nd to 3rd quartiles are boxed, 1st to 4th quartiles are dashed lines, statistical outliers to a normal distribution are circles.

Samples are labelled by "Subject No._Day_Hour"

## SUMMARY

- Fadraciclib was well tolerated from dose levels 1 to 5 (up to and including 100mg BID, M-F, week 1-4 in 28-day cycles) in patients with advanced solid tumors or lymphomas.
- No treatment-related Serious Adverse Events (SAEs), or SUSAR, or Dose-limiting Toxicities (DLTs) have been reported.
- Overall, unrelated serious TEAEs occurred in 8 patients (31%). Treatment-related TEAEs were reported in 19 patients (90.4%; 57.1% experienced grade ≥ 3).
- As of 30 Sep 2022, 21 patients were treated with fadraciclib in dose levels 1-5. The median treatment duration is 2.4 cycles (range 1-5 cycles).
- As of 30 Sep 2022, 18 patients (81.8%) discontinued treatment; among those, 9 patients (40.9%) discontinued due to disease progression.
- Two PRs have been observed in T-cell lymphoma patients. Four patients (cervical, endometrial, HCC, and ovarian cancer) showed target lesion reduction. A pancreatic cancer patient showed stable disease for 5 cycles.
- Plasma concentration of fadraciclib (CYC065) is dose proportional, crossing the target engagement threshold level with increasing duration at dose levels 4 and 5 after repeated oral administration.
- Enrollment continues at dose level 6 (150mg BID, M-F, week 1-4) as of Sep 2022.