CYCLACEL®

Translating cancer biology into medicines

Lytham Partners Virtual Investor Growth Conference
October 8, 2020

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Clinical Stage Value Drivers

Fadraciclib (CYC065) CDK inhibitor (i.v. and oral)

- Clinical proof of mechanism (MCL1 / cyclin E down-regulation & tumor shrinkage)
- Combination with venetoclax in R/R leukemias (AML/MDS, CLL)

Sapacitabine nucleoside analogue (oral)

- Unique DNA damage response mechanism for BRCA mutant patients with breast, ovarian and pancreatic cancers
- Combinations with venetoclax in R/R AML/MDS & olaparib in 2L BRCA mutant breast cancer

CYC140 PLK inhibitor (i.v. and oral)

- Compelling preclinical data in liquid & solid cancers; first-in-human study in progress

Regulation of MCL1 to Enable Apoptosis

MCL1 is one of ten most frequently amplified cancer genes[1]

Competitive race to develop drugs that suppress MCL1

Inhibiting protein directly is an option; but AMG397 MCL1 inhibitor on clinical hold

Inhibiting transcriptional CDK enzymes suppresses MCL1 and can reinstate apoptosis

OUR SOLUTION:

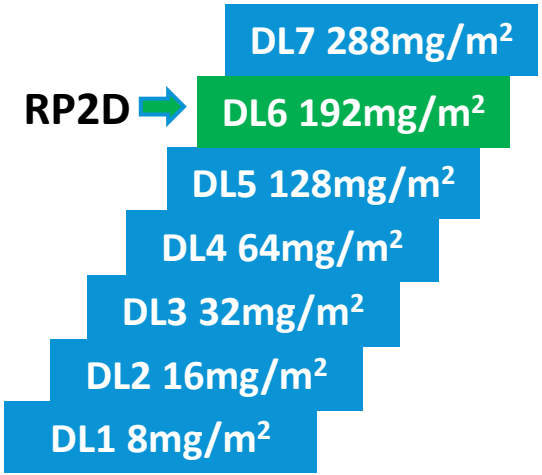
- **Fadraciclib** (a.k.a. **CYC065**, potent and selective CDK2/9 inhibitor with i.v. and oral forms)
- Designed based on clinical observations of activity of **seliciclib** (CYC202 first generation CDKi)
- We believe it is 1st Rx to show durable MCL1 suppression and anticancer activity in humans

[1] *Beroukhim R et al. Nature 2010.*

CYC065-01 Phase 1 Escalation Schema

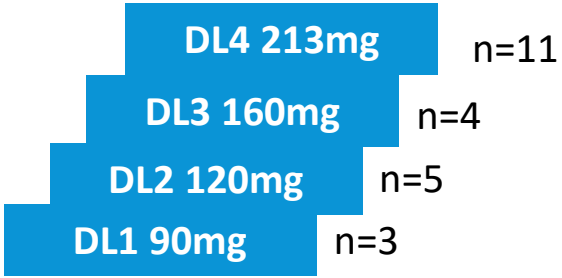
Part 1 i.v. n=26
4h, d1 3wk

(completed)



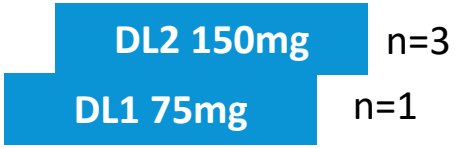
Part 2 i.v. n=23
1h, d1,2,8,9 3wk

(ongoing)



Part 3 p.o. n=4
QD, d1,2,8,9, 3wk

(ongoing)



Source: Cyclacel data on file.

Fadraciclib (CYC065) Clinical Efficacy Summary

Single Agent:

- MCL1, cyclin E or MYC amplified solid tumors; durable MCL1 suppression at tolerable doses (i.v. once q3 weeks); durable SD
- MCL1 amplified endometrial cancer (i.v. 4x q3 weeks): durable PR
- Cyclin E amplified ovarian cancer: SD with 29% tumor shrinkage

Combination with venetoclax:

- CLL: ↓ lymph node size and converted MRD +ve to MRD –ve
- AML/MDS: ↓ peripheral blast counts, TLS (200mg/m^2 i.v. day 1, 15)

Fadraciclib (CYC065) Clinical Safety Summary

Dosing:

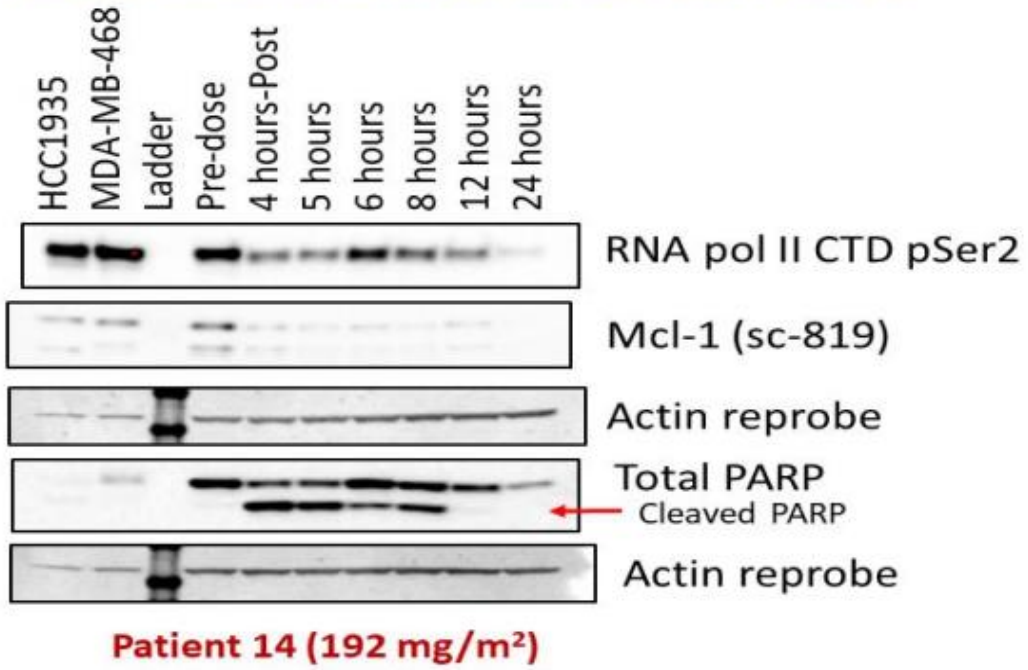
- 192mg/m^2 (~ 350-400mg) RP2D (i.v. once q3wk)
- 213mg (i.v. 4x q3wk): some creatinine ↑, dose reduction
- 150mg (p.o. and i.v.) daily schedules in progress

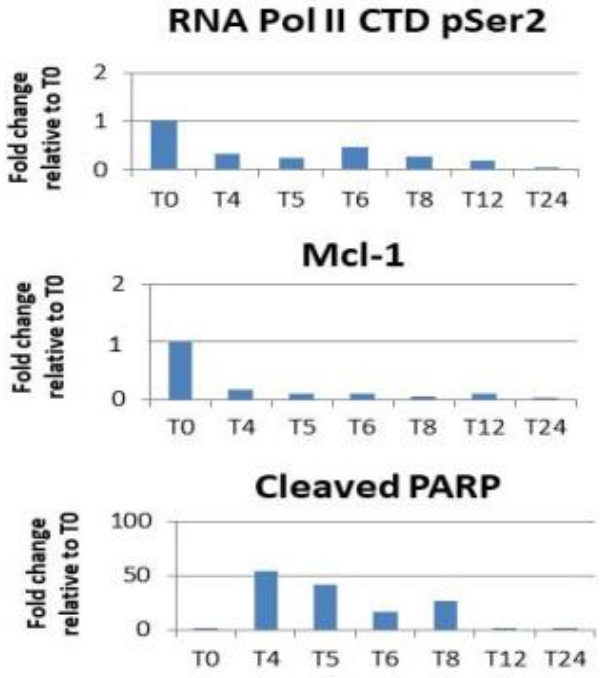
Toxicity:

- Solid tumors: ↓ WBC, renal observations
- Hem. Malignancies (AML/MDS): ↓ WBC, TLS (200mg/m^2 i.v. day 1, 15)

CYC065-01 Phase 1 part 1 Proof of Mechanism

Target inhibition detectable at 24 hours

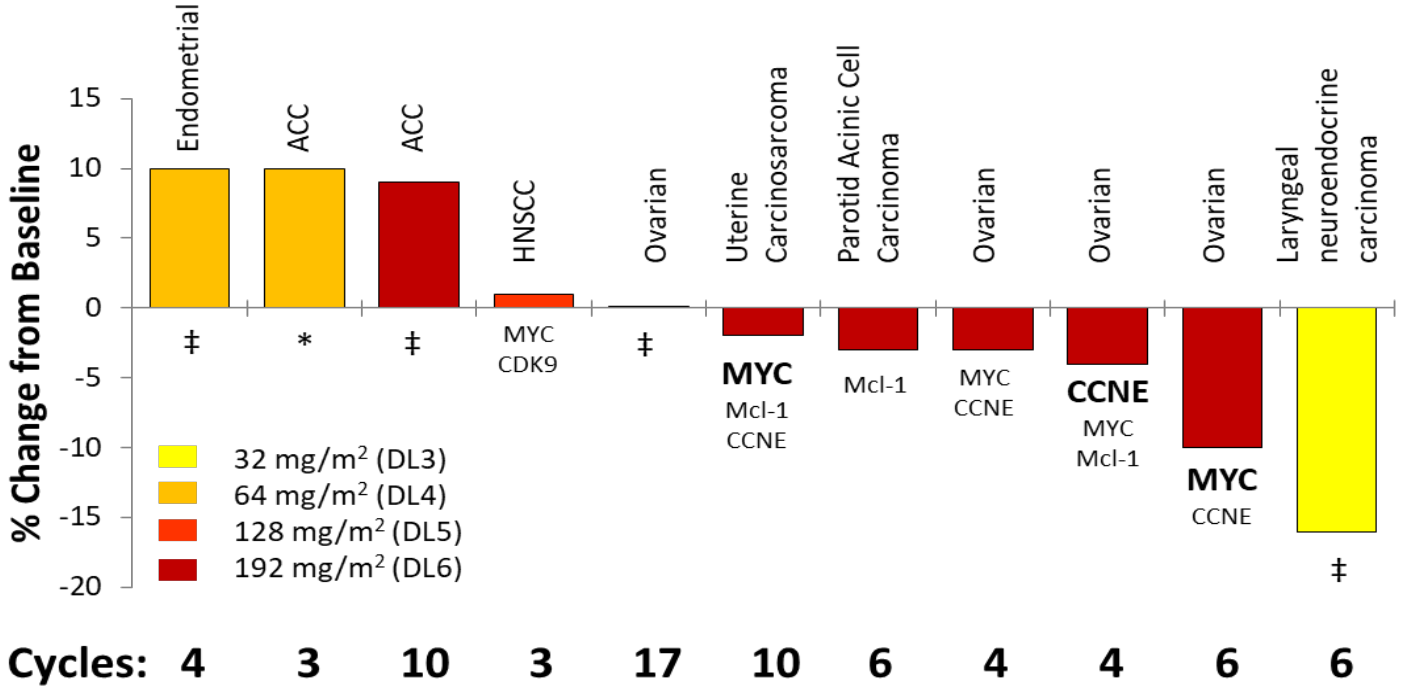




Source: Do, Khanh T., et al, AACR Annual Meeting 2018.

American Association for Cancer Research

CYC065-01 Phase 1 part 1 Activity



*‡ no information; * complex deletions/gains. High copy gains shown in bold.*

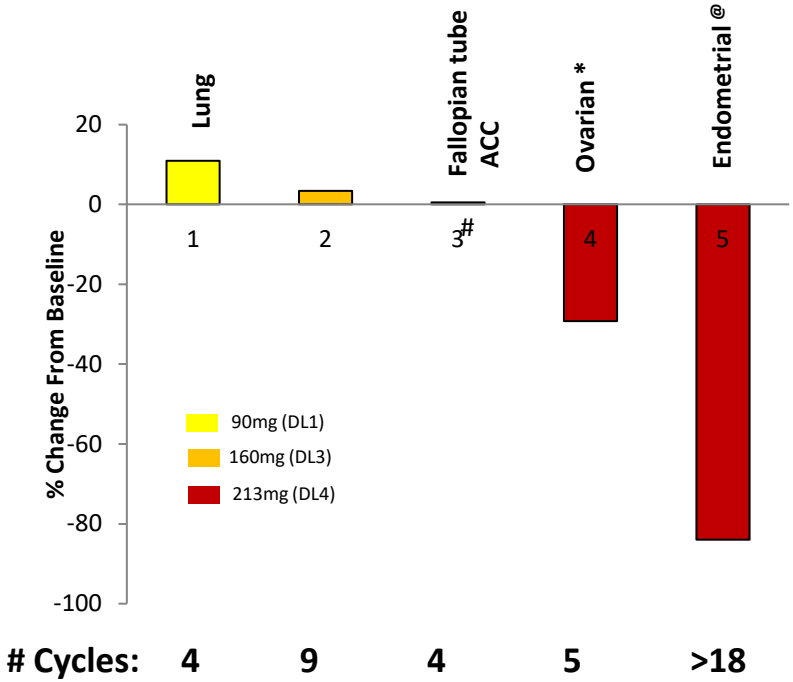
Source: Do, Khanh T., et al, AACR Annual Meeting 2018.

Summary:

- **20/26 patients evaluable for response per RECIST 1.1**
- **11/20 patients achieved stable disease (SD)**
- **6/11 patients achieved SD for 4+ cycles**

CYC065-01 Phase 1 part 2 Activity

Part 2 i.v. n=23; 1h, d1,2,8,9 3wk (ongoing)



At 213 mg, 1 confirmed PR and 1 confirmed SD:

@ PR at 4 cycles (MCL1 amplified endometrial; deepening response; now at >80% shrinkage at C18)

* SD > 4 cycles (Cyclin E amplified ovarian)

Source: Data on file. # Non-measurable target tumor lesion.

Rationale in R/R Leukemias

AML post venetoclax + HMA:

- MCL1 is major player; BCL2 less so: venetoclax modest single agent activity
- “Double-Hit” strategy to suppress MCL1 + BCL2

CLL post BTKi regimens; nearly all survivors receive 2L:

- Venetoclax does not ↓ MCL1 which is a major correlate of resistance
- “Double-Hit” strategy to suppress BCL2 + MCL1

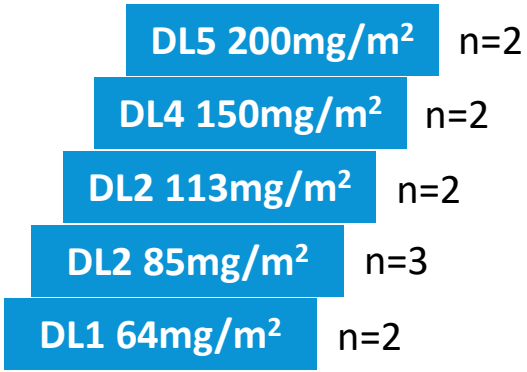
Preclinical evidence of synergy for venetoclax + CYC065

Source: Chen et al AACR 2018 Abs 5095; Cyclacel data on file.

CYC065-03 Phase 1 AML/MDS Activity

PART 1 i.v. n=11

…ongoing…



- MCL1 plays prominent role in AML
- Aim to suppress apoptotic pathways
- Combination with venetoclax post ramp-up
- Blast reductions in peripheral blood; TLS at DL5

Source: Cyclacel data on file.

CYC065-02 Phase 1 CLL Activity

PART 1 i.v. n=5

…ongoing…

- n=1 **DL4 150mg/m²**
- n=1 **DL3 113mg/m²**
- n=1 **DL2 85mg/m²**
- n=2 **DL1 64mg/m²**

- Achieved bone marrow MRD –ve after 4 cycles
- Achieved bone marrow MRD –ve after 6 cycles
- 2nd pat.; ibrutinib failure; lymphoadenopathy; PR on venetoclax ramp-up;
- Lymph node shrinkage after 5 cycles of 065+venetoclax
- Achieved peripheral blood MRD -ve

Source: Cyclacel data on file.

Tissue Agnostic Precision Medicine Strategy

Based on FDA approval of MRK's Keytruda in MSI high/MMR cancers

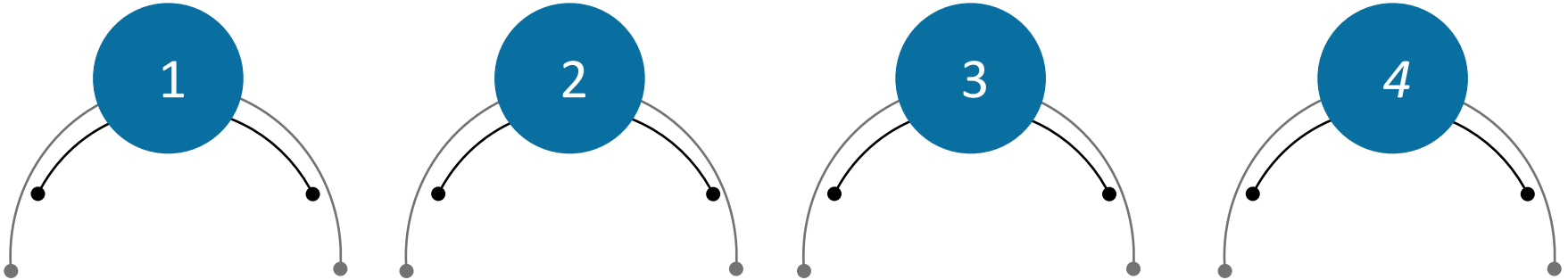
- MCL1 and/or Cyclin E amplified cancers
- Target ORR ~ 10-15% and DoR ~ 6 months
- Quotas to ensure enrollment in multiple histologies
- Add combinations with appropriate SoC

Basket Clinical Trials

- Multiple patient cohorts (defined by histology, etc.)
- Initially single agent
- Add combinations with appropriate SoC
- Depending on signal expand or drop cohort

Efficient use of patient and capital resources

Basket Study Design *(Phase 1b/2a)*



1	2	3	4
Ovarian	**Endometrial/ Uterine**	**Breast**	*Rare cancers*
Single agent	Single agent	Single agent	*MCL1 overexpressing NSCLC, HNSCC, sarcoma*
Combo w/ chemo &/or PARP inhibitor	Combo w/ IO or chemo &/or kinase inhibitor	CDK4/6 r/r Combo with Hormonal therapy	*Single agent* *Combo w/ IO*

Fadraciclib is Addressing Large Markets

HGSOC 2L

- 27k US incidence; ~79k prevalence
- CCNE1 is 35% of US BRCA1/2 wt CCNE1 and BRCA1/2 m CCNE1 amplified

Endometrial/Uterine 2L

- 5k US incidence; ~77k prevalence
- CCNE1 is 20% of high grade serous which is 50% of total

Breast HR+ 2L

- 56k US incidence; ~735k prevalence
- CCNE1 is 30% of HR+ which is 73% of total

Breast Cancer BRCA1/2+

- 18k US incidence; ~238k prevalence
- CCNE1 is 40% of BRCA+ which is 17% of total

Source: SEER Database

CDK & MCL1 Inhibitor Landscape

CDK2/9 transcriptional isoforms enabling apoptosis:

CYC065 (CDK2/9, CYCC) Ph1 data

BAY1251152; *atuveciclib BAY'572* **(CDK9, BAY)** Ph1 data

AZD4573 (CDK9, AZN) Ph1 ongoing

Other (pan CDK or selective):

flavopiridol/alvocidib (pan CDK, SUM) Ph2

dinaciclib (pan CDK, MRK) Ph3 terminated

voruciclib (CDK4/6/9, MEIP) Ph1 data

SY1365 (CDK7, SYRS) Ph1 data

MCL1 inhibitors:

AMG176 i.v./**AMG397** oral - Clin. hold

S64315 (Servier, Ph1b ven combo AML)

AZD5991 (FiH Ph 1).

AZ poster AACR 2019: *CDK9i targeting MCL1: Antitumor responses with AZD4573 strongly correlate with selective MCL1 inhibitors, such as AZD5991. CDK9i targets other labile pro-survival proteins beyond MCL1 such as Bfl-1 (a.k.a. BCL2A1).*

Source: data on file; Boiko S et al AACR 2019.

MD Anderson-Cyclacel Alliance

- Up to 170 patients with single agent or combinations of: CYC065, CYC140, sapacitabine
- Risk Sharing: MD Anderson assumes patient costs; Cyclacel supplies drugs and limited support
- Payments to MD Anderson upon First Commercial Sale in indications studied

COVID-19 Viral Pneumonia-“Flattening the Curve”

Cytokine storm & severe hypoxia in intubated patients lead to rapid decline & death

Clinical correlates of mortality in COVID-19 patients[1]:

- Old age; sepsis; d-dimer> 1µg/mL; ↑ IL-6, CRP, LDH; troponin I and lymphopenia

Need to dampen overactive immune response mediated by activated neutrophils

Neutrophil survival is promoted by MCL1[2]

Source: [1]Ruan Q, et al, IntensCareMed, 2020 doi.org/10.1007/s00134-020-05991. Zhou F et al Lancet 395 10229 1054. [2]Rossi A, et al, Nature Med 2006 Sept; 12(9):1056.

Role of CDK Inhibitors in COVID-19 Pneumonia?

Transcriptional CDK inhibitors co-regulate immune response via transient neutrophil apoptosis

- **seliciclib** induces MCL1 downregulation and enables apoptosis of inflammatory neutrophils[1]
- **seliciclib** inhibits transcription and secretion of IL-6 in multiple myeloma cells[2]
- **seliciclib** is more effective than IL-6-neutralizing antibody at suppressing IL-6 induction of MCL1[2]
- seliciclib in IST in patients with refractory rheumatoid arthritis (TRAFIC study).

Source: [1]Rossi A, et al, Nature Med 2006 Sept; 12(9):1056. [2]Raje N, et al, Blood, 2005 Aug 1; 106(3):1042.

Uni. of Edinburgh-Cyclacel Collaboration

- Agreement to test effects of both **fadraciclib** and **seliciclib** in enabling apoptosis in inflammatory neutrophil cells
- Early peripheral blood neutrophil response associated with poor outcome in COVID-19
- Part of broader STOPCOVID project funded by LifeArc ($2.5m)
- If positive, include in adaptive clinical trial to test PoC

THE UNIVERSITY of EDINBURGH

Key Milestones

- Updated **fadra** Ph 1 safety, PK, efficacy data with frequent dosing schedule in patients with advanced solid cancers;
- Initial safety, PK data from Ph 1 study of **fadra** oral formulation;
- FPI **fadra** Ph 2 tissue agnostic precision medicine study;
- Initial safety, PoC data from **fadra**-venetoclax Ph 1 in R/R AML/MDS & CLL;
- Initial data from **sapacitabine**-venetoclax Ph 1/2 study in R/R AML/MDS;
- Initial data from **CYC140** Ph 1 First-in-Human study in R/R leukemias; and
- Data from Phase 1b/2 **sapacitabine**-olaparib IST in BRCA mutant metastatic breast cancer when reported by the investigators.

Investment Thesis

Clinical stage, state-of the-art oncology programs

Targeting molecularly-defined patient populations

Overcome cancer cell resistance & DNA repair

CDK inhibitors: validated drug class

Competitively positioned

Significant market opportunities

THANK YOU

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