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Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of CYC065, a Cyclin-Dependent Kinase Inhibitor, in Patients with Advanced Cancers (NCT02552953)

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Disclosure Information

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Presented by: Khanh Do, M.D.

The presenter has no financial relationships to disclose.
This presentation will not be discussing off-label use.

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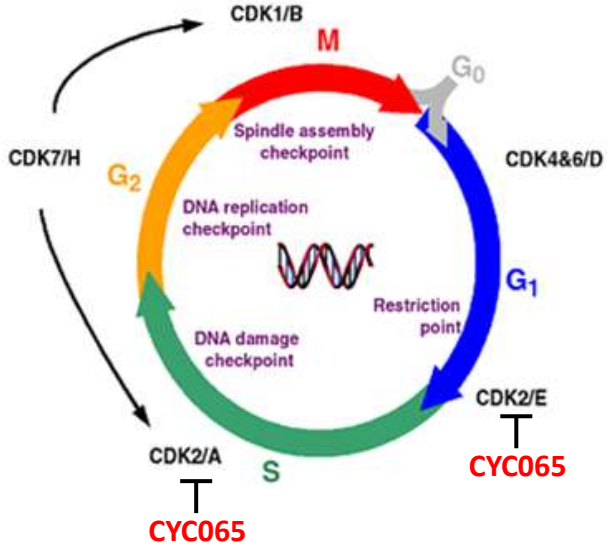
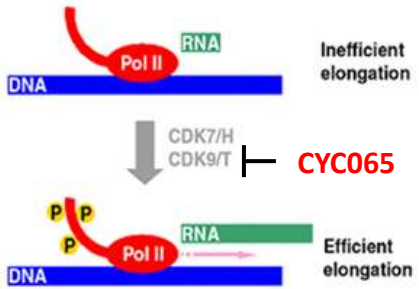
Overview: Cyclin Dependent Kinases



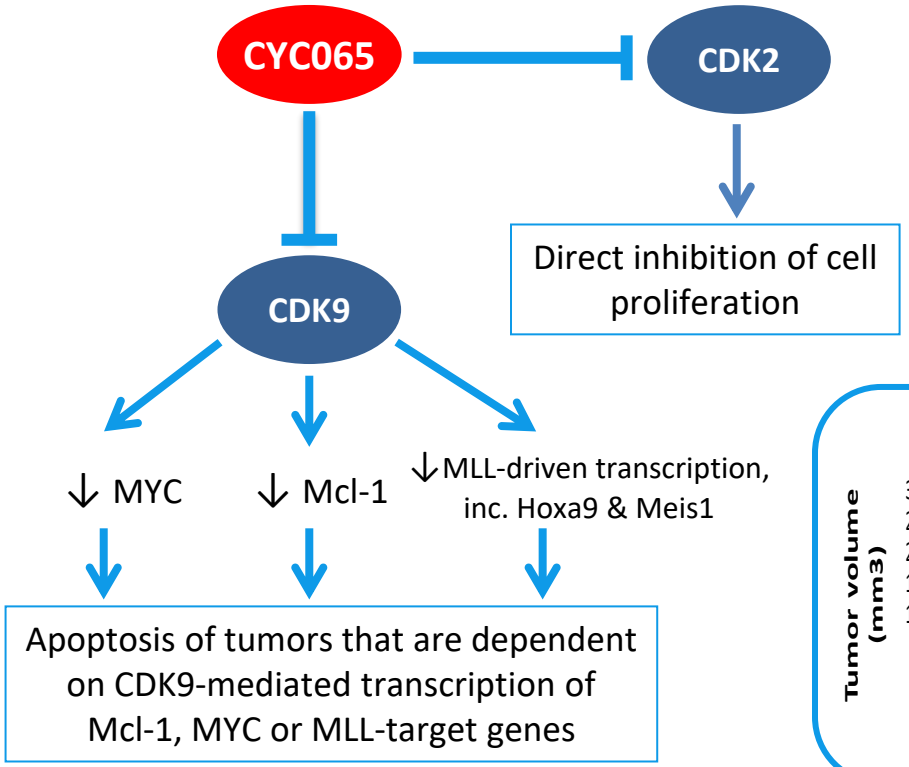


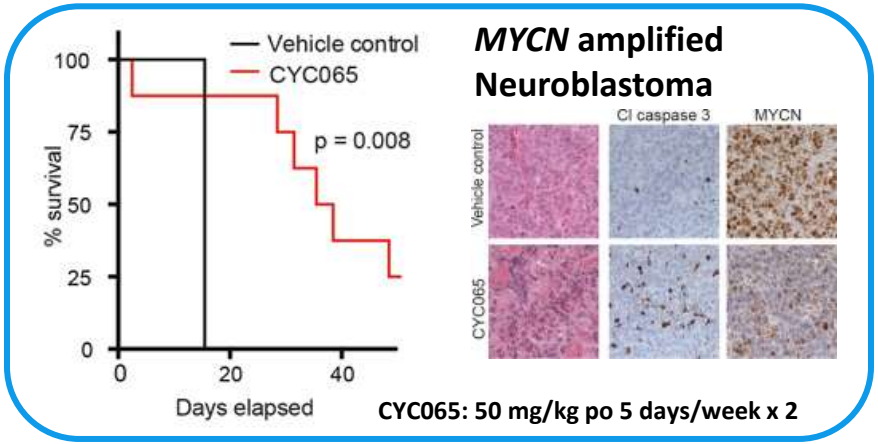
- Cell cycle dysregulation is a hallmark of cancer, central role in cell proliferation and survival
- Cyclins/cyclin dependent kinases (CDKs) are involved in regulation of the cell cycle: CDK 1, 2, 4, 6, 7 (CAK)
- CDK 7, 8, 9, and 12 also regulate gene transcription through phosphorylation of RNA Pol II

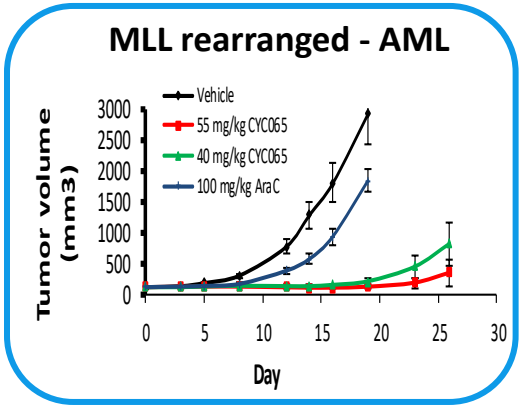
- **CYC065** is a 2nd generation aminopurine inhibitor of CDK2 and CDK9
  - *In vitro* kinase potency (IC_{50}) :
    CDK2 = 5 nM; CDK9 = 26 nM

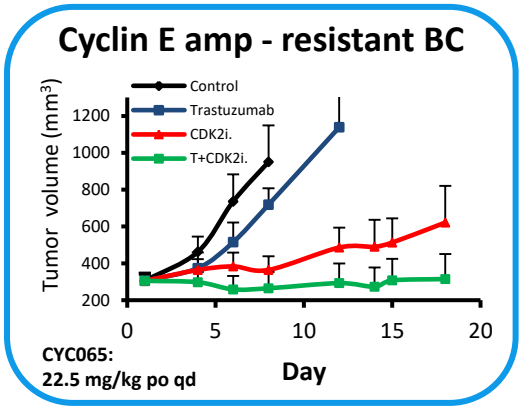
Preclinical Overview

Key targets: Mcl-1, MYC, cyclin E, MLL









(Poon et al. 2016; Saladino et al. 2015; Scaltriti et al. 2011)

Study Objectives and Design

Primary Objective:

- To determine MTD and recommended phase II dose (RP2D)

Secondary Objectives:

- To evaluate pharmacokinetics
- To assess pharmacodynamic markers (RNA Pol II CTD P-Ser2 and Mcl-1 levels in PBMCs)

Design:

- Open label, single arm, dose escalation study in patients with advanced solid tumors
- CYC065 administered by i.v. infusion over 4 hours every 21 days
- Dose escalation: 100% (< Gr2 toxicity); 50% (first Gr2 toxicity); 25% (first DLT)

Key Eligibility Criteria and Dose Limiting Toxicity Criteria

Key Inclusion Criteria:

- Advanced solid tumors progressed on standard therapies or have no known effective therapy
- ECOG PS 0 – 1
- Evaluable disease
- Adequate organ function:
  - Absolute neutrophil count $\geq$ 1.5 x 10^9/L, platelets $\geq$ 100 x 10^9/L
  - Total bilirubin $\leq$ 1.5 x ULN, ALT $\leq$ 1.5 x ULN
  - Creatinine $\leq$ 1.5 x ULN or creatinine clearance > 60 mL/minute (Cockcroft formula)

Key Exclusion Criteria:

- Untreated CNS metastases or evidence of CNS progression on MRI within 4 weeks prior to enrollment for treated CNS metastases

Dose Limiting Toxicity:

- Grade 3 or 4 non-hematological toxicity (except alopecia, inadequately treated nausea, vomiting and diarrhea)
- Grade 3 or 4 AST/ALT with Grade 2 elevation of bilirubin
- Neutropenic fever or grade 4 neutropenia > 5 days
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding
- Grade 4 anemia
- Treatment delay > 2 weeks due to drug-related adverse events

Maximum Tolerated Dose (MTD): the highest dose level at which less than 2/6 patients experience DLT in cycle 1

Recommended phase 2 dose (RP2D): the dose level at which less than 1/3rd of patients experience a DLT during cycle 1 in a confirmatory expansion cohort

Patient and Disease Characteristics

		Number of patients (n=26)
Age	Median (range)	63 (43 - 71)
ECOG	0	6
	1	20
Gender	Male	5
	Female	21
Histology	Ovarian (papillary, serous, transitional)	14
	Uterine (carcinosarcoma, endometrial)	4
	HN (SCCHN, carcinoid, adenoid cystic)	6
	Pancreatic	1
	CRC	1

Common Adverse Events

(All cycles, maximum grade, regardless of causalities, n=26)

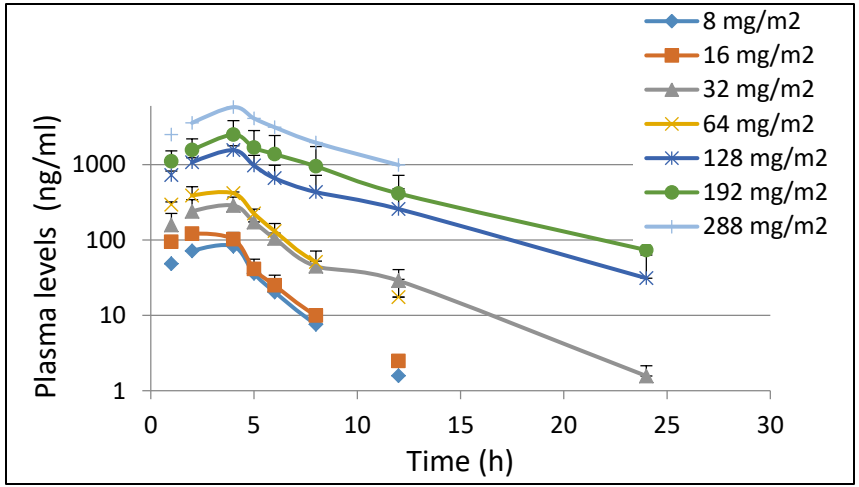
	Grade 1-2	Grade 3-4
Leukopenia	5	4
Neutropenia	2	4
Abdominal pain	5	3
Constipation	8	-
Diarrhea	15	3
Nausea	14	1
Vomiting	11	1
Fatigue	9	2
Decreased appetite	8	1
Dehydration	9	1
Hypophosphatemia	5	1
Dizziness	6	-

Dose-Limiting Toxicities

Dose mg/m^2	Number of patients treated (n=26)	DLT
8	1	-
16	2	-
32	2	-
64	3	-
128	4	-
192 (RP2D)	13	n=1: Gr 3 diarrhea n=1: Gr 3 diarrhea with hypomagnesemia Gr 3 febrile neutropenia, WBC lysis with Gr 3 hypocalcemia, ALT, AST, bilirubin elevations Gr 4 leukopenia and thrombocytopenia, Gr 3 mucositis and dehydration
288	1	n=1: Gr 4 neutropenia, Gr 3 febrile neutropenia

Pharmacokinetic Analysis

CYC065 exposure in plasma



- **Exposure increases with dose**
- **Half-life: 1.6 – 3.9 h**
- **RP2D (IV): Avg C_{max} ~ 6 µM; AUC_{inf} ~48 h*µM**
- **50 mg/kg mouse (oral): Avg C_{max} ~ 5.5 µM; AUC_{inf} ~8 h*µM**

PK parameters – NCA, WinNonlin 7.0™

Dose in mg/m^2 (n)	Half-life (h)	C_{max} (ng/ml)	AUC_{inf} (h*ng/ml)	Vz (L)	CL (L/h)
8 (1)	1.64	83	376	96	40
16 (2)	1.84	121	549	146	54
32 (2)	3.20	287	1660	163	36
64 (2)	1.94	451	2160	147	53
128 (4)	3.78	1550	10400	135	25
192 (12)	3.90	2490	18900	143	29
288 (1)	3.67	5770	38300	67.3	13

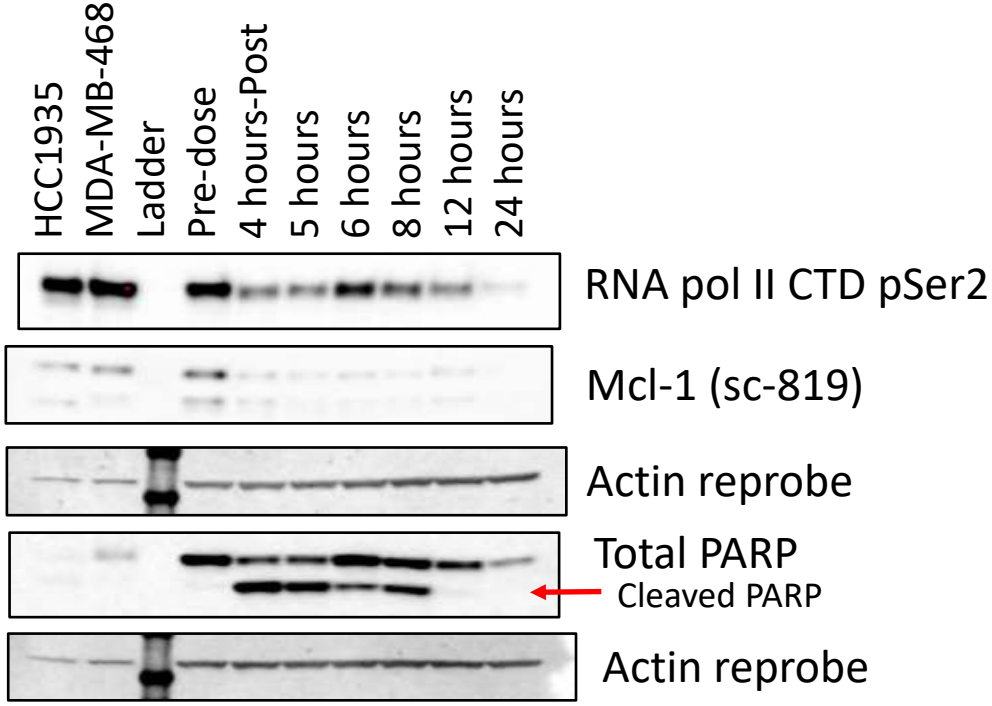
Pharmacodynamic Analysis

Dose (mg/m^2)	n	# pts with 24hr ↓ Mcl-1
8	1	0
16	2	0
32	2	1
64	3	1
128	4	2
192	13	11
288	1	1

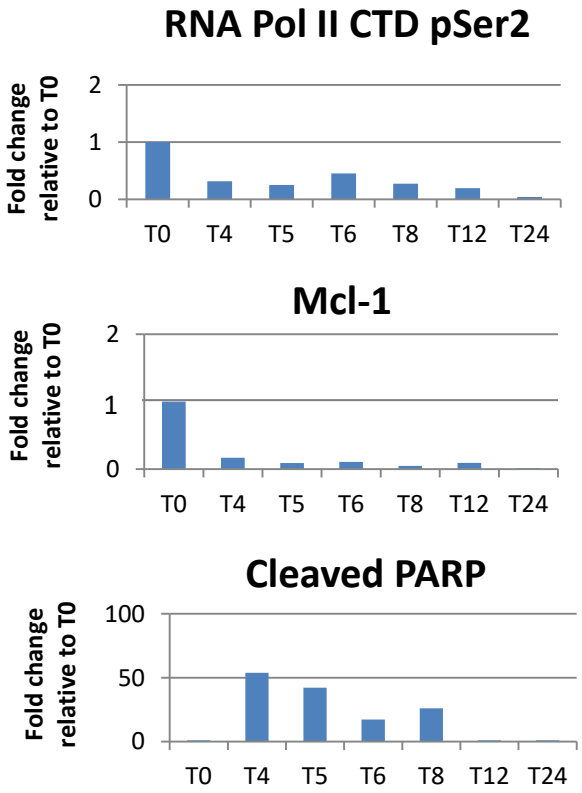
All patients with prolonged stable disease had durable target inhibition

Pharmacodynamic Endpoints

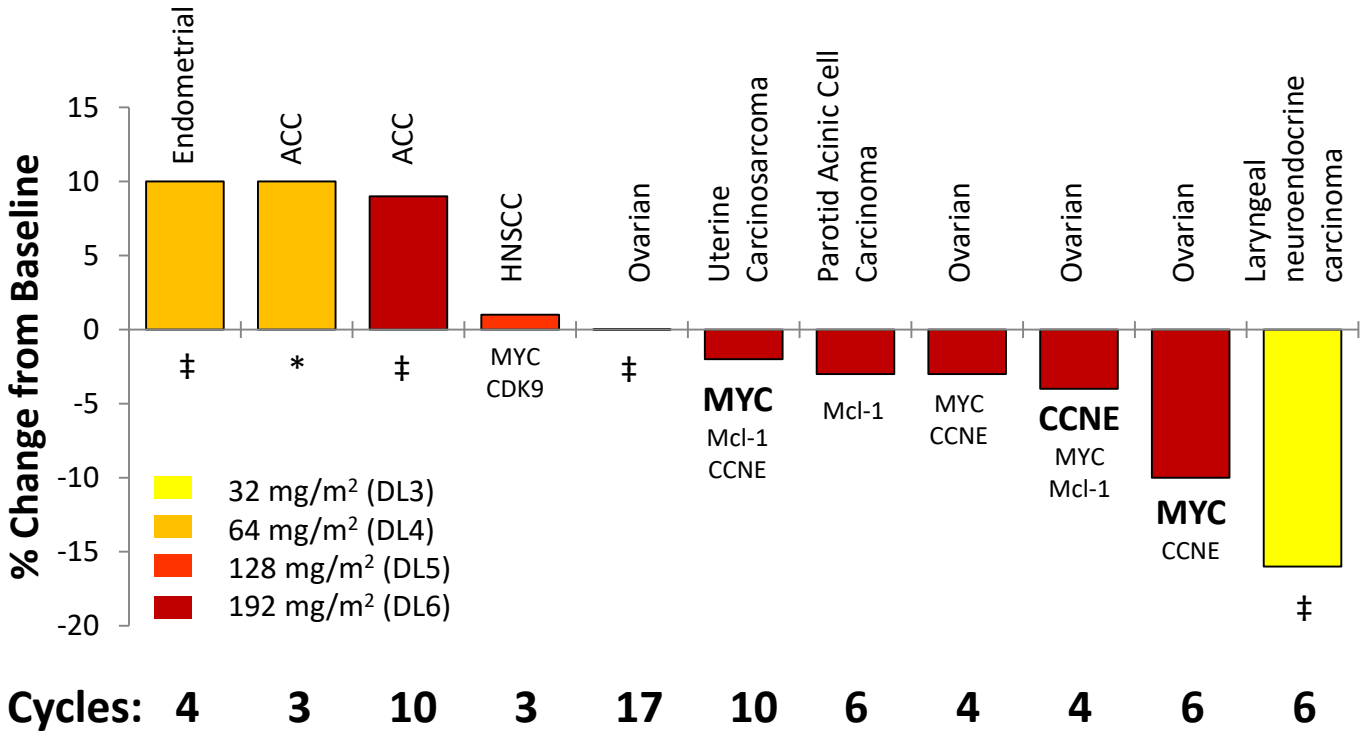
Target inhibition detectable at 24 hours



Patient 14 (192 mg/m^2)



Clinical Response



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

Summary:

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

Summary

- RP2D for 4-hour infusion once every 3 weeks is 192 mg/m^2
- CYC065 exposure increases with dose
  - Half-life: 1.6 – 3.9 h
  - Average C_{max} at RP2D: ~ 6 µM
- Pharmacodynamic suppression of Mcl-1 detectable at 24 hours after dosing at RP2D
  - Response on study correlated with durable target inhibition
- Stable disease was best response, longest response ~1 year

Future Plans

- Evaluate more dose intense schedule
- Oral formulation under development
- Evaluate efficacy in Mcl-1, *MYCN*, or cyclin E amplified cancers
- Durable Mcl-1 suppression could synergize with Bcl-2 inhibition in triggering tumor cell death via apoptosis
  - providing strong rationale to combine CYC065 with venetoclax

R Chen, et al: Strategic combination of the cyclin-dependent kinase inhibitor CYC065 with venetoclax to target anti-apoptotic proteins in chronic lymphocytic leukemia.
Abstract Number: 3905. McCormick Place South, Exhibit Hall A, Poster Section 38.
Tuesday April 17, 2018, 8:00 AM - 12:00 PM CT.

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