CYCLACEL®

Translating cancer biology into medicines

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Clinical Stage Value Drivers

Fadraciclib (aka CYC065) CDK2/9 inhibitor (i.v. and oral)

Clinical proof of mechanism i.v. as a single agent

1st to show durable MCL1 suppression & anticancer activity in patients

Phase 1b/2 oral in registration enabling, multiple cohorts to start 1H 21

CYC140 PLK1 inhibitor (i.v. and oral)

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

Phase 1b/2 oral in registration enabling, multiple cohorts in planning

CDK Inhibitor Landscape

CDK9 → transcriptional regulation of anti-**apoptotic** proteins MCL1, MYC …

CDK2 → cell cycle checkpoint regulation of cyclin E (*CCNE*)

Aim: restore apoptosis (CDK2 inhibition enhances apoptosis by CDK9 inhibition)[@]

*CDK4/6 → cancer cell **senescence***

- *$5 bn class (palbociclib, abemaciclib, ribociclib)*
- *Palbociclib failure stat sig correlated with cyclin E ↑ (PALOMA-3)**

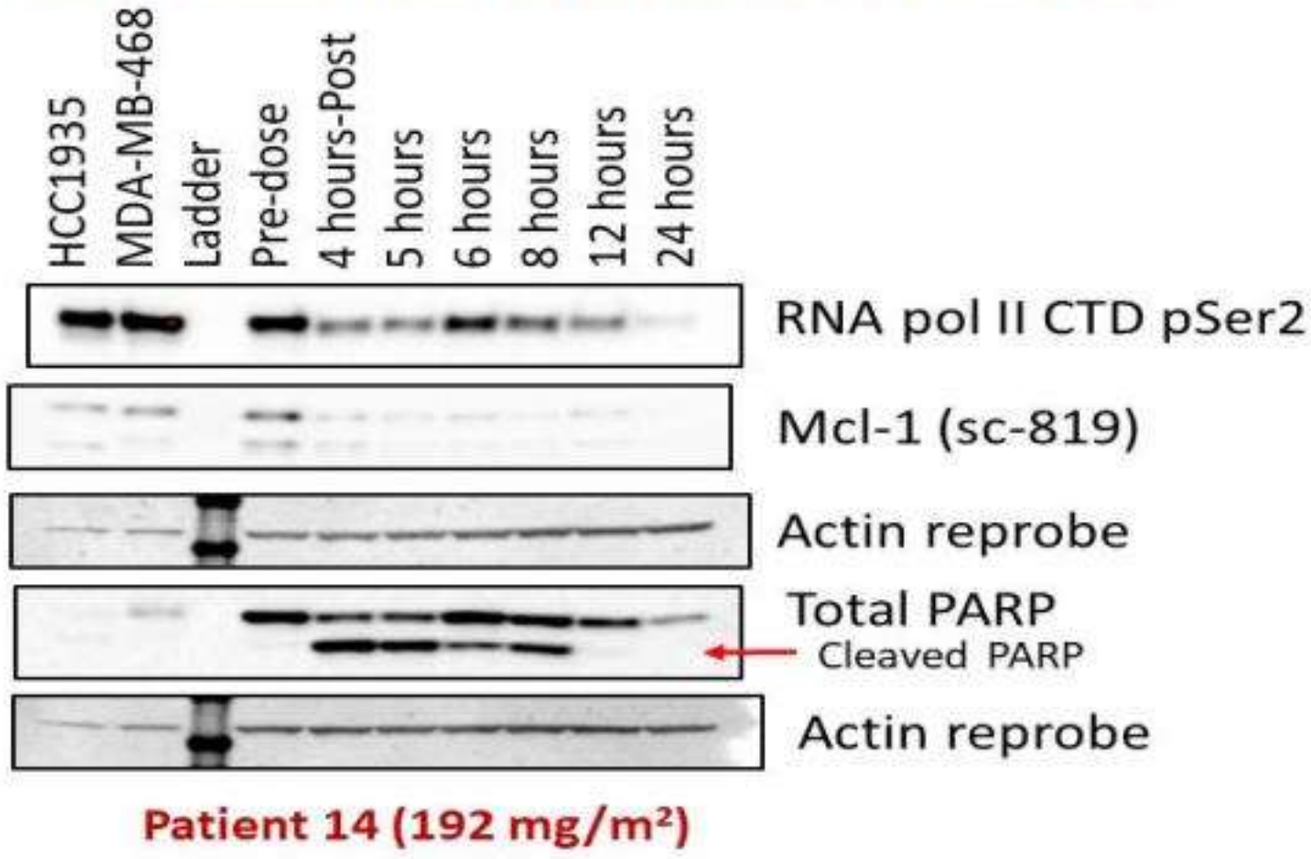
*Source: [@]Roghani, ASCO 2020 Abs e16056. Poon E et al, JCI 2020_doi.org10.1172JCI134132. *Turner NC et al; JCO 2019 .*

Fadraciclib Early to Mid-stage Development

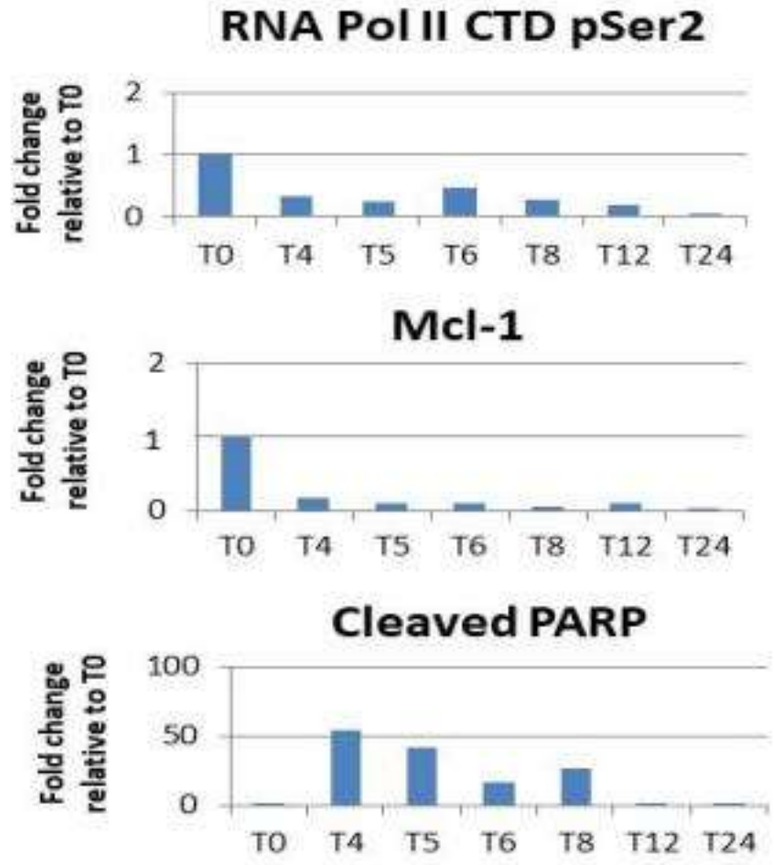
- ✓ **Low intensity schedules** (Ph 1 i.v.; once q3 wk; 4x q3 wk)
  - ✓ Single agent; tolerability, short half-life, PK/PD markers 'on mechanism', durable PR and SD in advanced solid tumors
  - ✓ With venetoclax: antileukemic activity, incl. ↓ lymph nodes, MRD +ve to –ve conversion; R/R CLL and AML
  - ✓ Oral bioavailability reported at ENA (Triple Meeting) 2020
- ▪ **High intensity schedules** (single agent, oral, Ph 1b/2 to start in 1H 21)
  - ▪ Prespecified statistical success rules, registration enabling design
  - ▪ Multiple expansion cohorts to explore activity in solid tumors, later leukemias
  - ▪ Combinability with relevant MoA drugs

CYC065-01 Phase 1 part 1 Proof of Mechanism

Target inhibition detectable at 24 hours



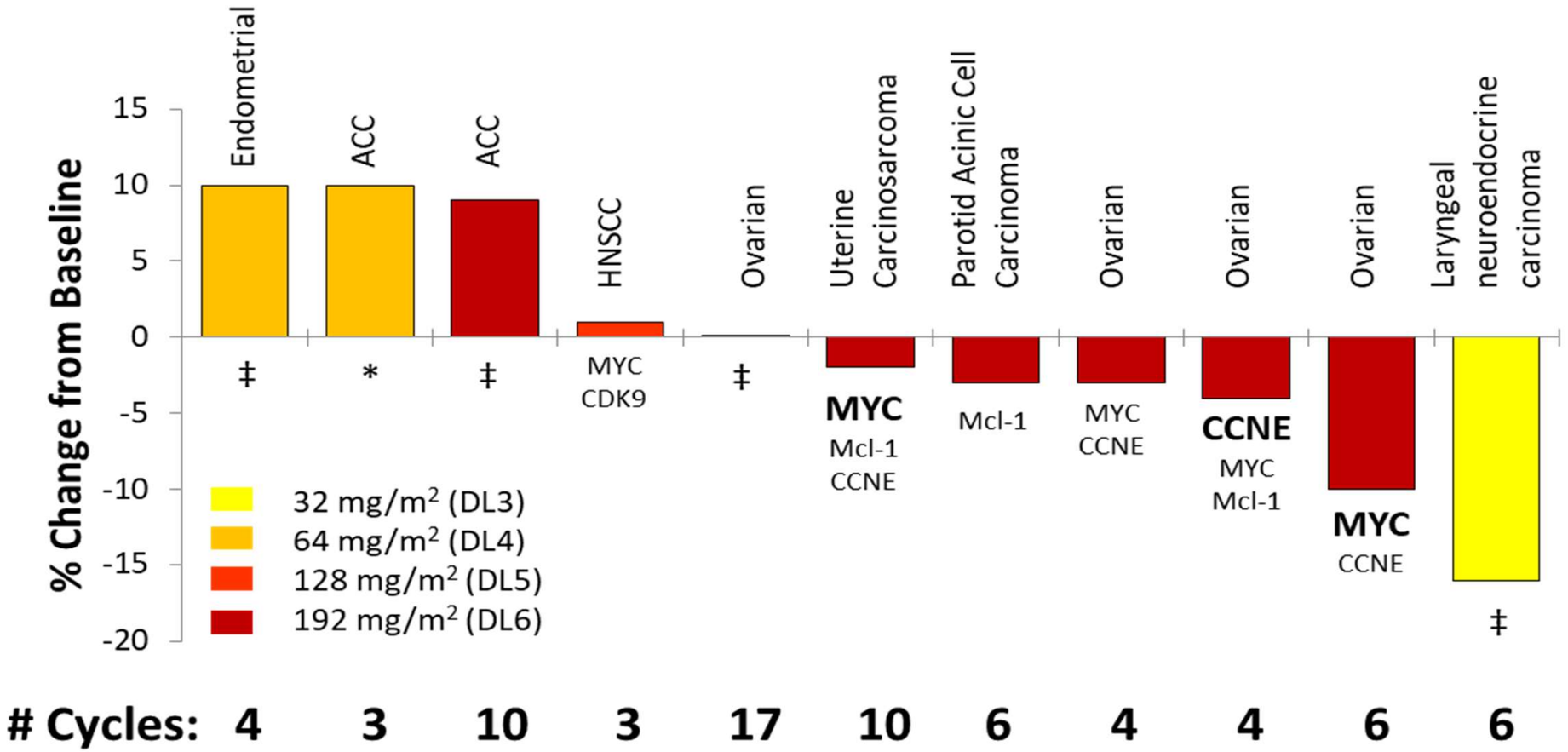
Patient 14 (192 mg/m²)



Source: Do, Khanh T., et al, AACR Annual Meeting 2018. RP2D = 192mg/m²

American Association for Cancer Research

CYC065-01 Phase 1 part 1 Activity



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

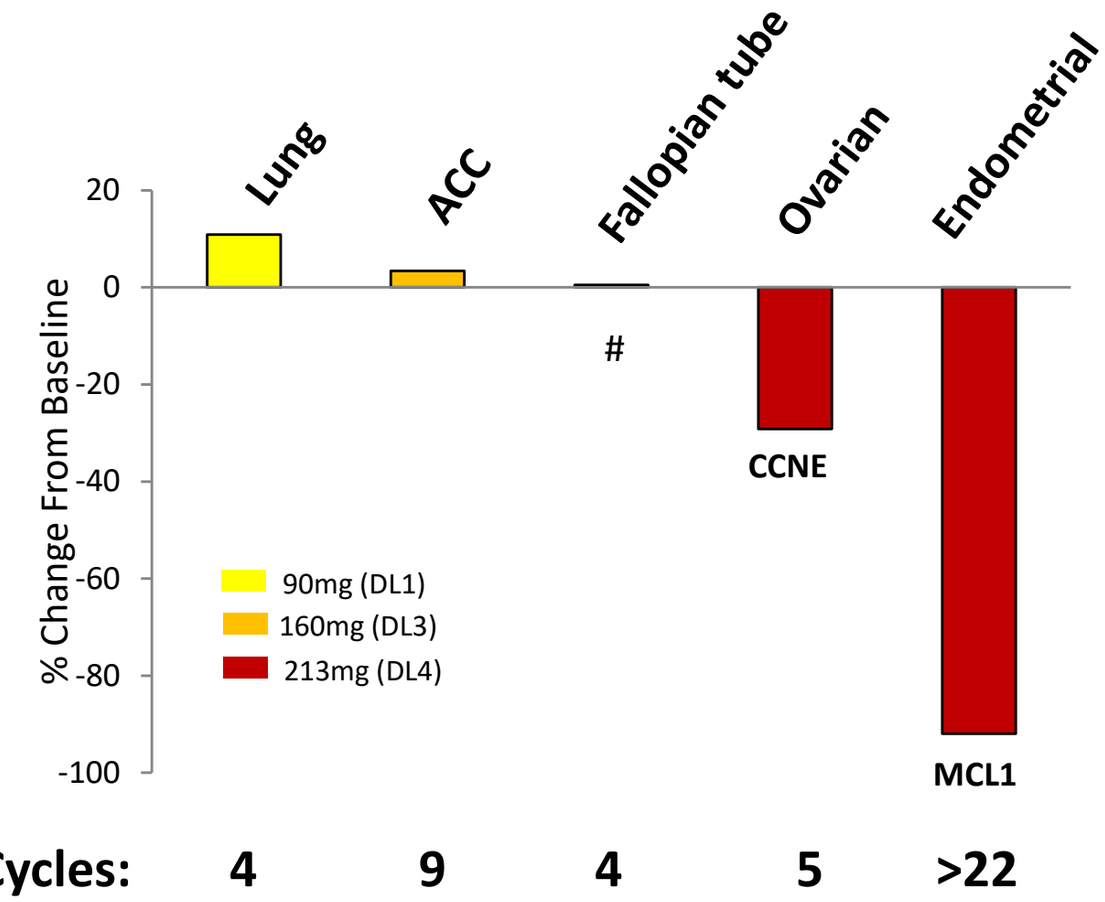
Source: Do, Khanh T., et al, AACR Annual Meeting 2018.

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=25; 1h, d1, 2, 8, 9; 3wk

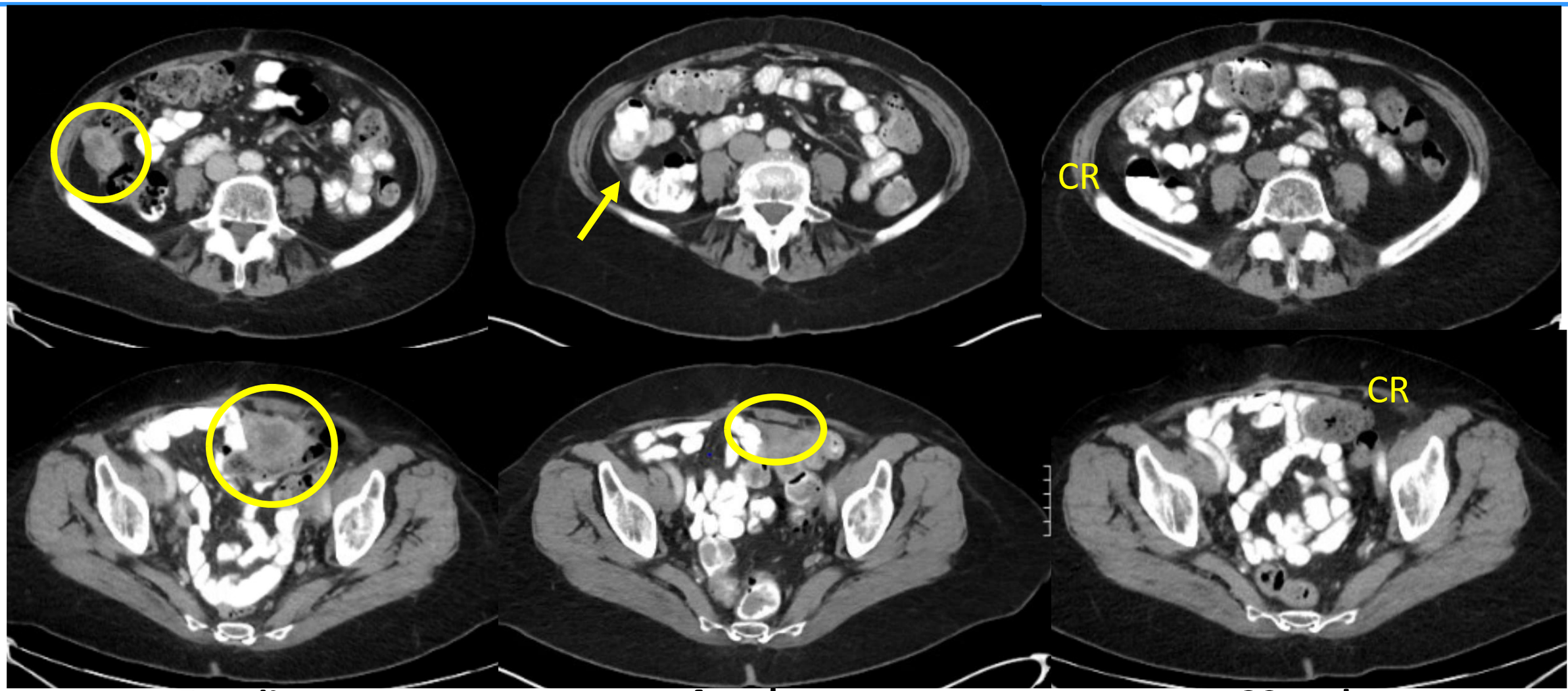


Source: Data on file. # Non-measurable target tumor lesion

At 213 mg, 1 confirmed PR and 2 SD were observed

- PR at 4 cycles (MCL1 amplified endometrial; deepening response; >96% shrinkage at C23)
- SD >4 cycles (Cyclin E amplified ovarian)

PR in MCL1 Amplified Endometrial Patient

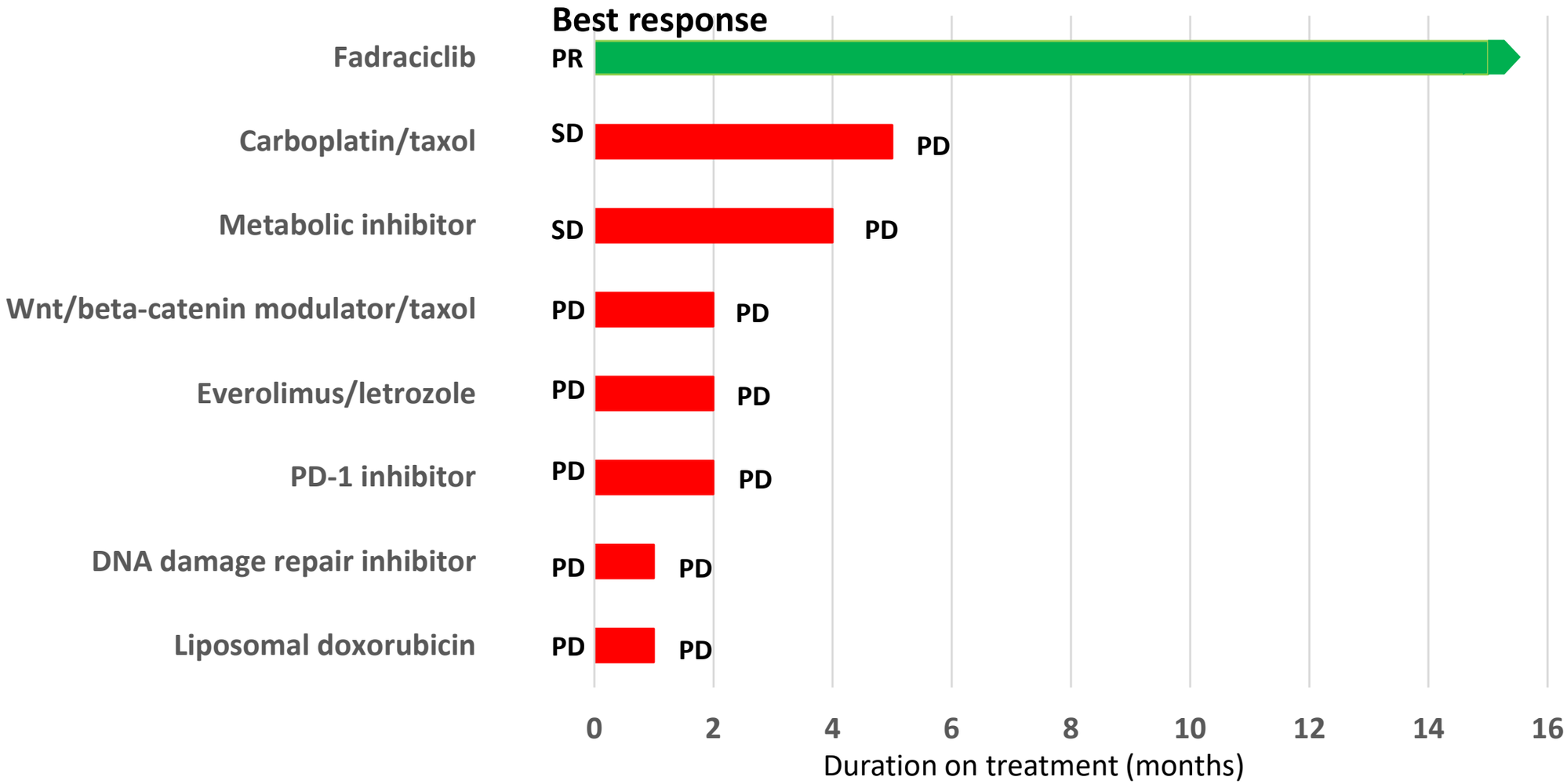


Baseline **4 cycles** **20 cycles**

Do, KT, et al, 2nd EORTC/AACR/NCI Virtual Symposium 24-25 October 2020.

Fadraciclib Most Efficacious Treatment

(endometrial adenocarcinoma patient with MCL1 amplification)



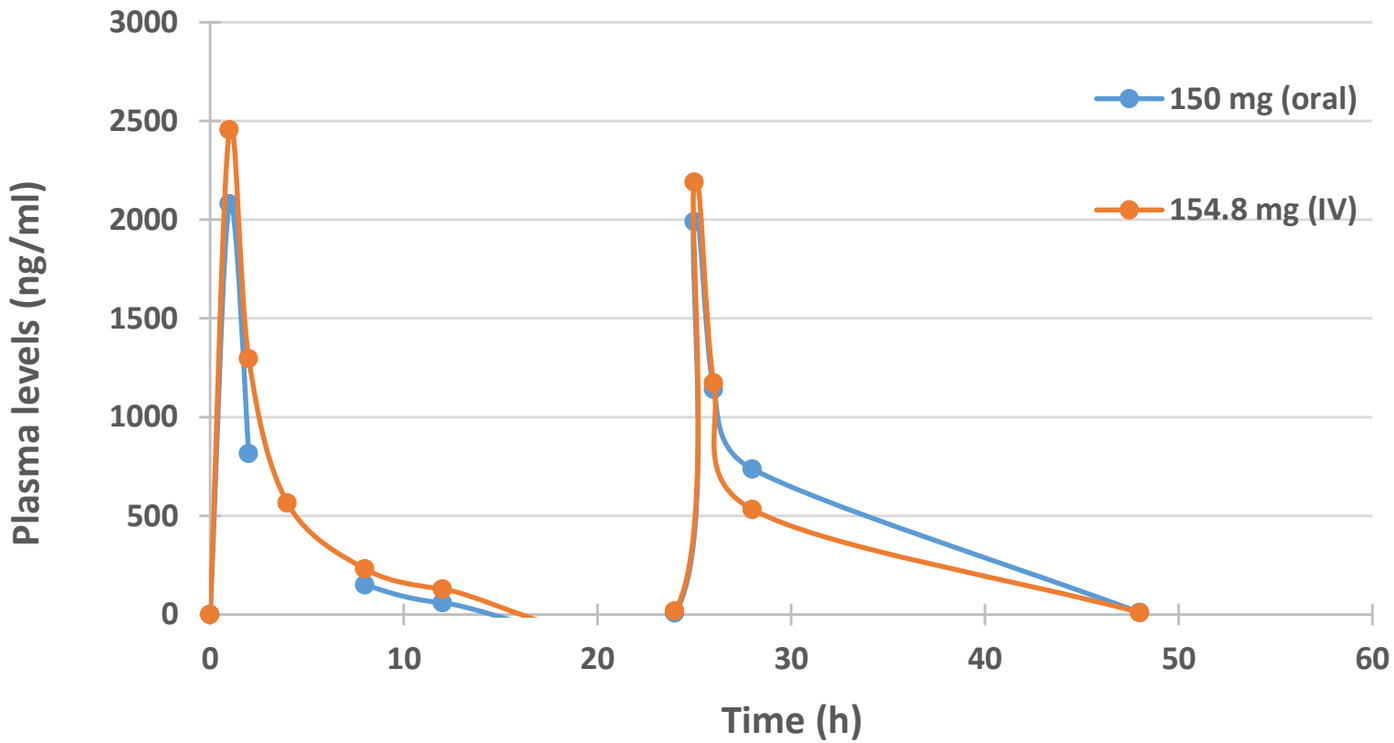
Source: Do, KT, et al, 2nd EORTC/AACR/NCI Virtual Symposium 24-25 October 2020. PD=progressive disease.

Fadraciclib High Oral Bioavailability

Oral dosing regimen: qd on days 1, 2, 8 and 9 every 3 weeks; ongoing

Cohort	Day 1		
	Half-life	C_{max}	AUC_{inf}
(mg)	(h)	(ng/ml)	(h*ng/ml)
150 Free Base equivalent (oral)	3.97	2080	6250
154.8 Free base equivalent (IV)	3.51	2460	8190

Fadraciclib plasma levels after oral and 1h-IV infusion



Source: Do, KT, et al, 2nd EORTC/AACR/NCI Virtual Symposium 24-25 October 2020.

CYC140 Summary

Optimized oral PLK inhibitor with short half life

Improved kinase selectivity

Favorable PK, increased dosing flexibility

Broad single agent preclinical activity

- Supports potential single agent clinical activity

Streamlined, registration-directed development strategy

PLK1: Key Mitotic Regulator and Oncogene

Oncogene with key role in regulation of

— mitotic entry and exit

— spindle formation

— cytokinesis

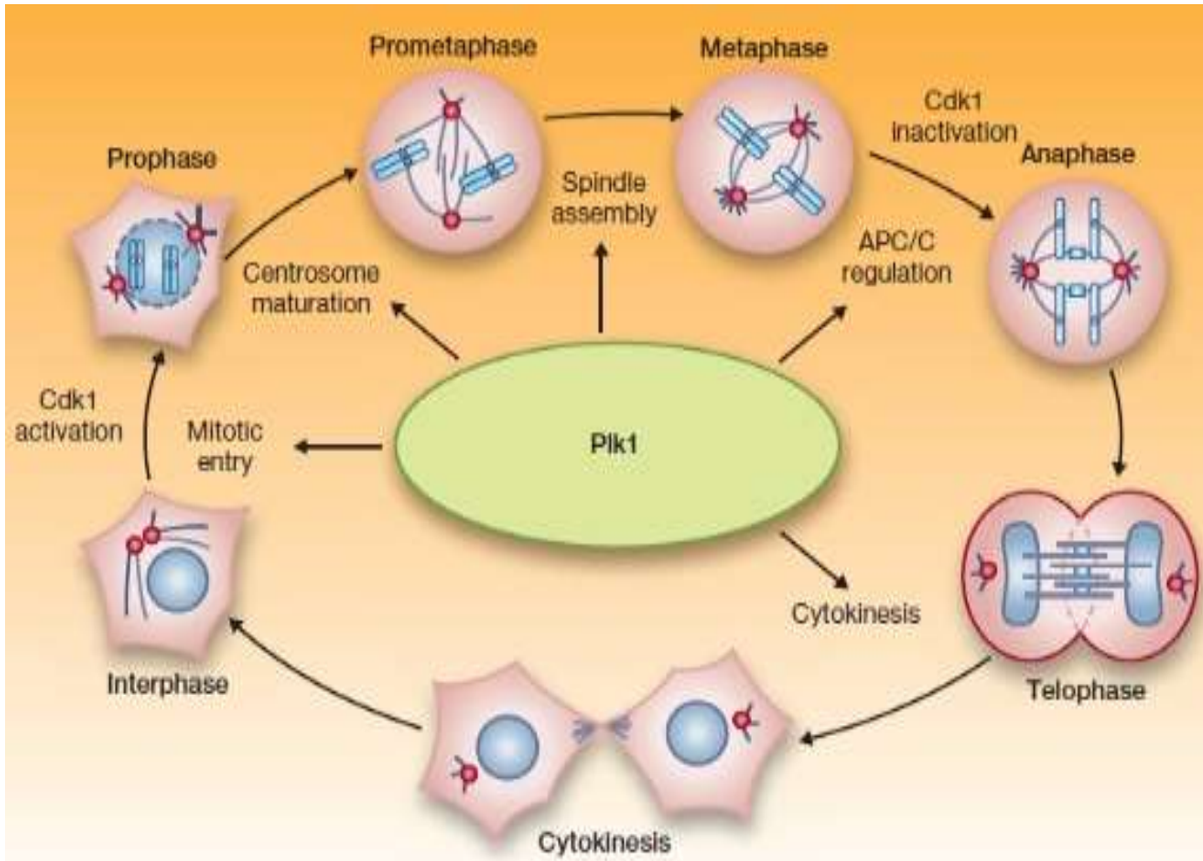
Cancer cells are very sensitive to PLK1 depletion, esp.

— mutated KRAS

— blocks proliferation by prolonged mitotic arrest

— onset of cell death in cancer cells

— normal cells with intact checkpoints less sensitive

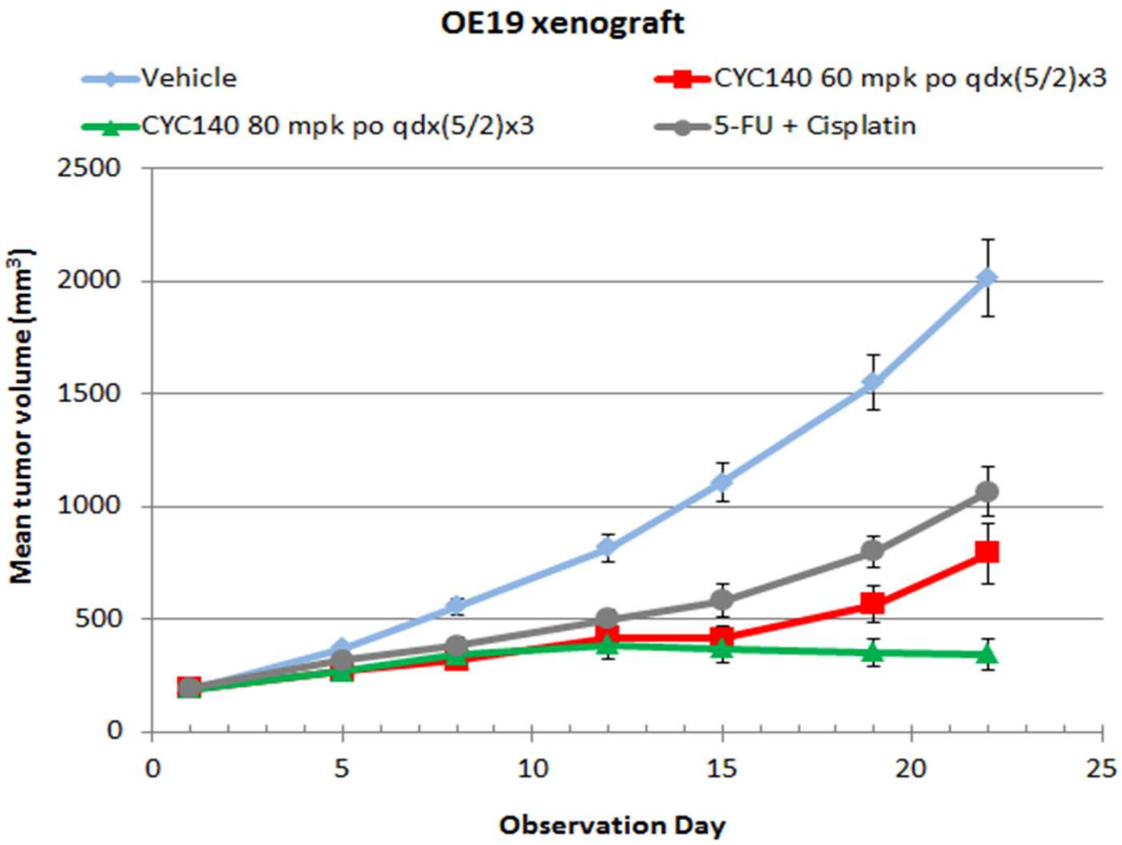


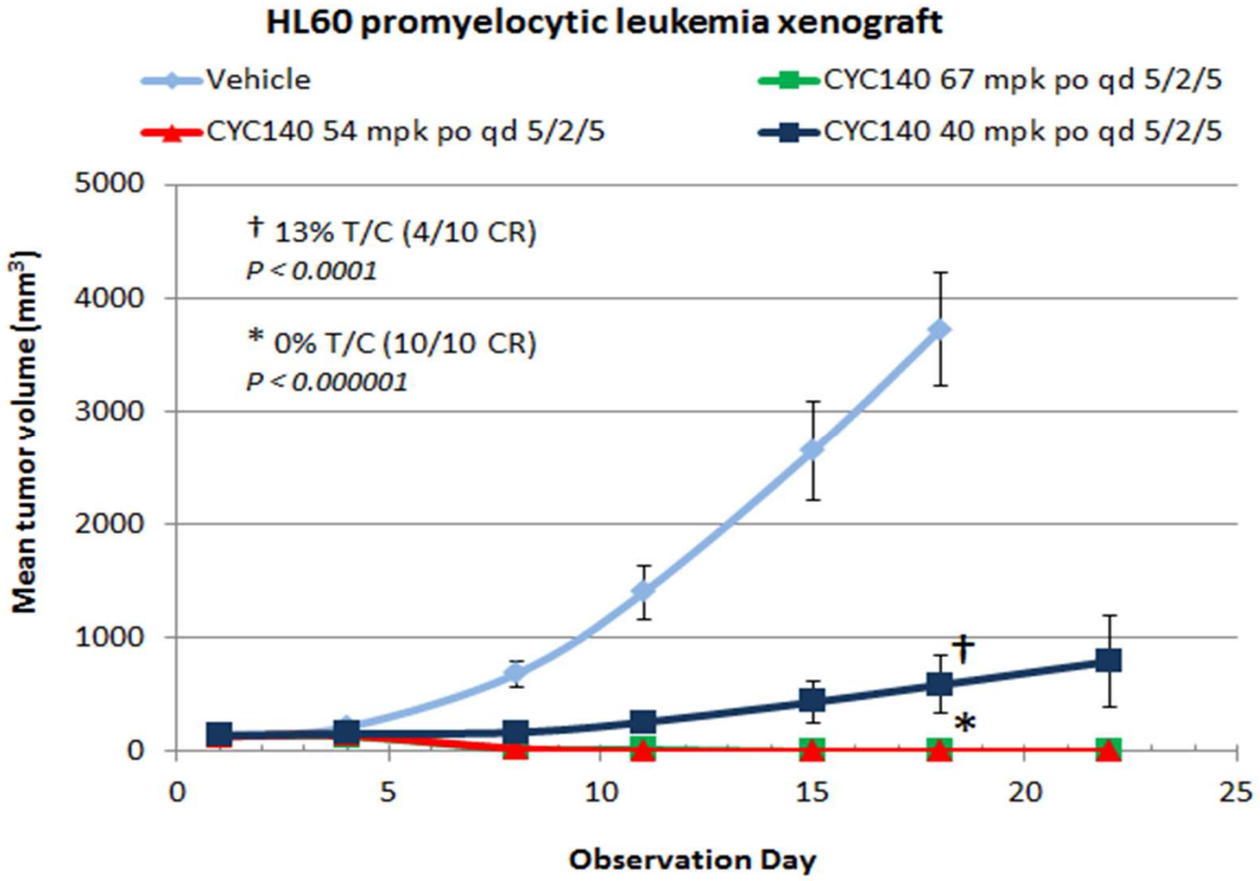
Medema RH et al. (2011) Clin Can Res 17(20):6459-66

CYC140-01 PLK1 inhibitor

Phase 1 FiH study opened, n=6 enrolled

Potent and selective inhibitor (PLK1 IC_{50} ~ 3 nM)





Source: Cyclacel data on file. FiH=First in human.

PLK Inhibitors

- ✓ **Volasertib**
  - ✓ BTD in AML Ph2 data; but Ph3 POLO-1 in AML imbalance of deaths
  - ✓ Dose intensity led to single agent activity; long terminal half-life ~110h
- **Onvansertib** (selectivity mainly PLK1, secondarily CDK9, etc.)
  - Signal in KRASmut mCRC with bevacizumab/FOLFIRI; terminal $t_{1/2}$ ~24h
  - Ph 1b studies in AML with chemo; prostate with abiraterone
- **CYC140** (selectivity mainly PLK1, secondarily PLK2, PLK3 family)
  - Preclinical activity in multiple solid tumors and leukemias; terminal $t_{1/2}$ ~11h
  - Unremarkable toxicity i.v. thus far
  - Aim: oral, dose intense, Ph 1b/2 in multiple solid tumors and leukemia cohorts

Source: data on file and Valsasina B et al Mol Can Ther 2012 11 1106-1016; https://mct.aacrjournals.org/content/11/4/1006.figures-only.

Financial Position & Capitalization

Proforma cash & cash equivalents September 30, 2020: $30.0m [1]

Operating cash burn (annual; excludes non-cash items)

- ✔ 2016: ~ $10.1m [2]
- ✔ 2017: ~ $ 7.5m [2]
- ✔ 2018: ~ $ 6.7m [2]
- ✔ 2019: ~ $ 9.4m [2]

Fully diluted shares: 12.2 million[3]. No debt

Estimated capital to early 2023

1. *$23.1m (10Q) + $6.9m (RD December 2020)*
2. *10K*
3. *Common stock outstanding 5.4m, preferred stock 1.2m, common stock warrants 5.0m, stock options 0.6m*

Key Milestones

- FPI orally-administered **fadra** in Ph 1/2 advanced solid tumor study;
- Initial safety, antileukemic activity data from **fadra**-venetoclax Ph 1 in R/R AML & CLL;
- Initial safety, PK data from Ph 1 study of **fadra** oral formulation;
- Initial data from **CYC140** Ph 1 First-in-Human study in R/R leukemias;
- Initial data from **sapacitabine**-venetoclax Ph 1/2 study in R/R AML/MDS; 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 & mitosis

CDK inhibitors: validated drug class

Competitively positioned

Significant market opportunities

THANK YOU

Cyclacel Pharmaceuticals, Inc.

200 Connell Drive #1500
Berkeley Heights, NJ 07922
+1 (908) 517 7330

Contact: ir@cyclacel.com