CYCLACEL®

Translating cancer biology into medicines

March 15, 2021
33rd Annual Roth Conference

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Clinical Stage Value Drivers

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

- Demonstrated i.v. clinical proof of mechanism as a single agent
- 1st CDK2/9i to show durable MCL1 suppression & anticancer activity in patients
- Streamlined Phase 1b/2 oral solid tumor study to start 1H21; multiple cohorts, registration enabling (MCL1, CCNE, MYC amplified)

CYC140 PLK1 inhibitor (i.v. and oral)

- Optimized oral PLK inhibitor with short half life
- Compelling preclinical data in liquid & solid cancers
- Streamlined Phase 1b/2 oral solid tumor study to start 2H21; multiple cohorts, registration enabling (PLK1, MYC amplified, KRAS mutated)

CDK Inhibitor Target Profile

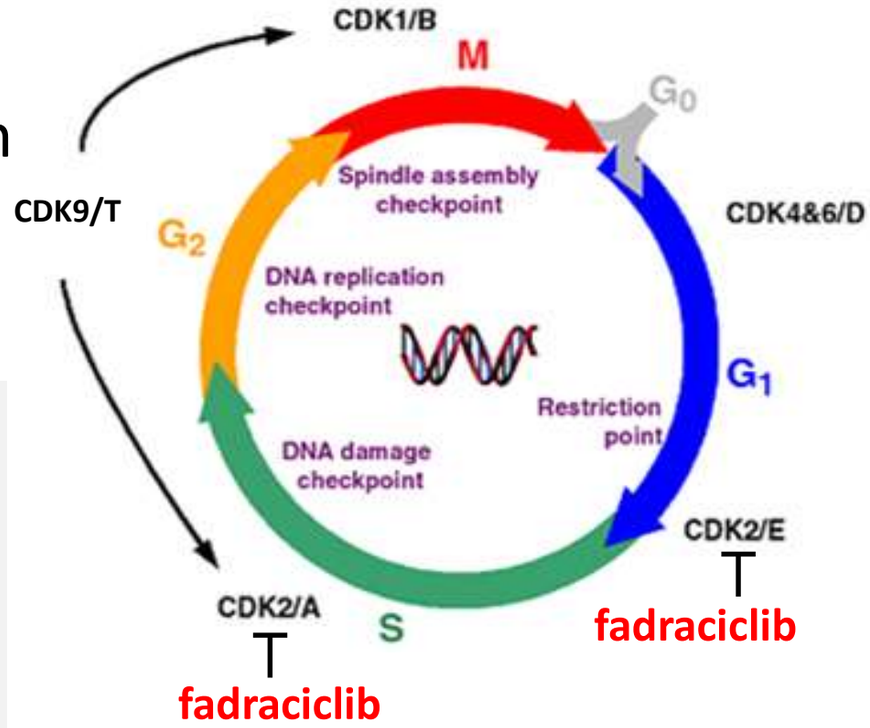
CDK9 → transcriptional regulation of anti-**apoptotic** proteins, MCL1, MYC …

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

Aim: **restore apoptosis** (CDK2i enhances apoptosis by CDK9i)[@]

CDK4/6 → validation

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



*[@] Somarelli, JA et al, Mol Cancer Ther 2020;19:2516. Poon E et al, JCI 2020_doi.org10.1172JCI134132. *Turner NC et al; JCO 2019.*

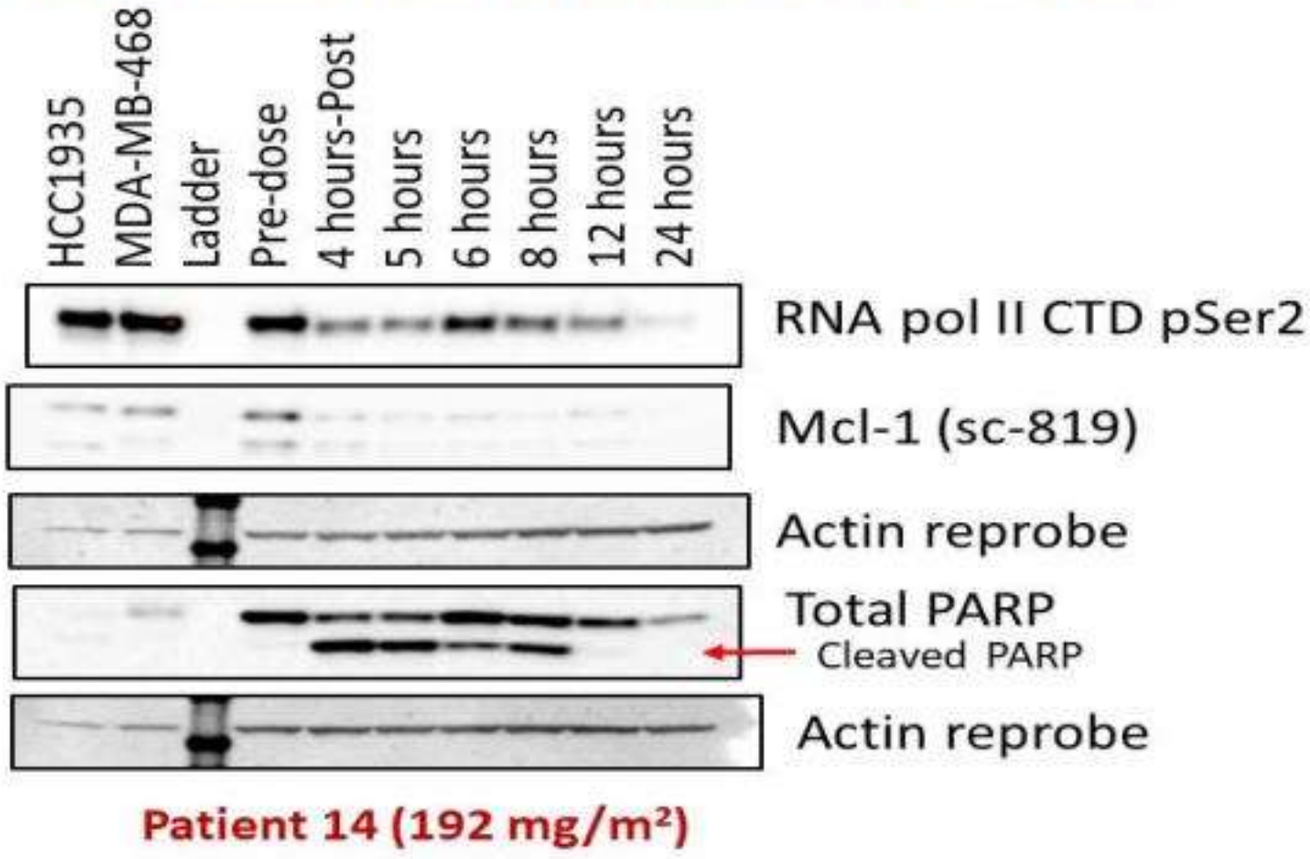
Fadraciclib Early to Mid-stage Development

- ✓ **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; Oral bioavailability at ENA (Triple Meeting) 2020
  - ✓ With venetoclax: antileukemic activity, incl. ↓ lymph nodes, MRD +ve to –ve conversion; R/R CLL and AML
- **Optimized biological dosing** (Ph 1b/2, oral schedule TBD; start in 1H21)
  - Prespecified statistical success rules, registration enabling design
  - Multiple expansion cohorts to explore activity in solid tumors, later leukemias
  - Single agent; combinability with relevant MoA drugs

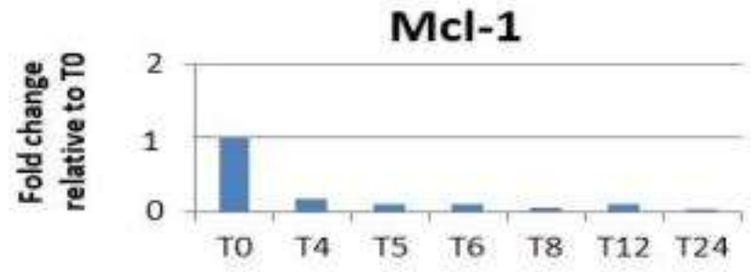
TBD = To be disclosed.

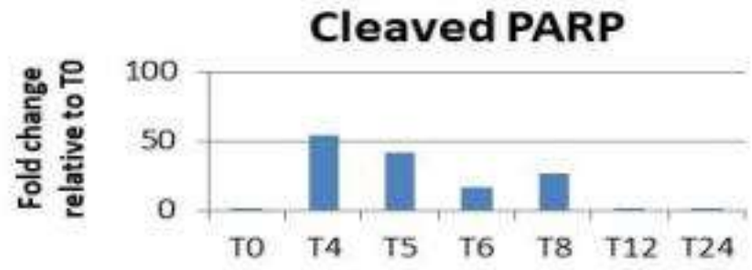
CYC065-01 Phase 1 part 1 Proof of Mechanism

Target inhibition detectable at 24 hours



Patient 14 (192 mg/m²)

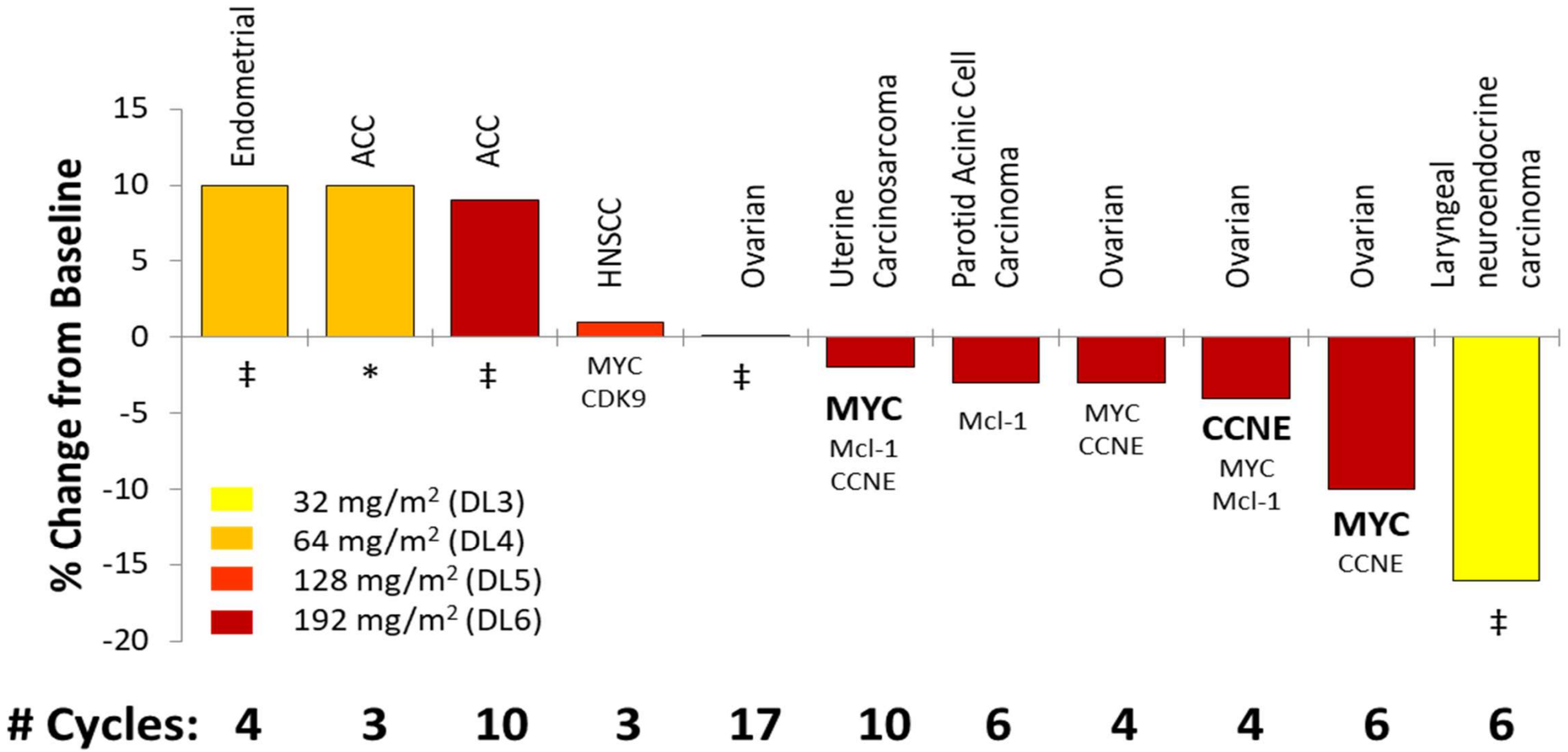




Do, Khanh T., et al, AACR Annual Meeting 2018. RP2D = 192mg/m².

American Association for Cancer Research

CYC065-01 Phase 1 part 1 Activity



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

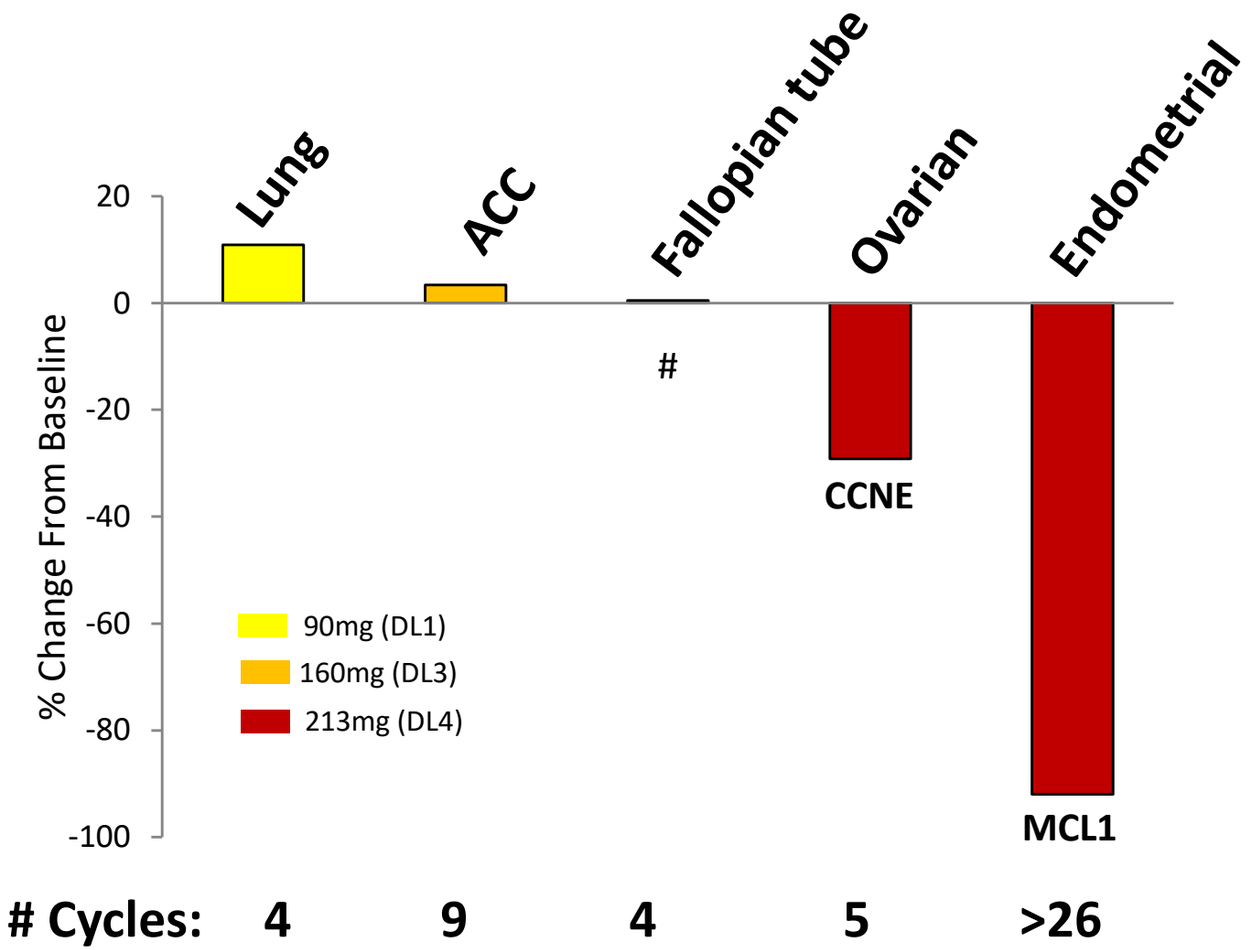
Do, Khanh T., et al, AACR Annual Meeting 2018.

i.v. once q3 wk:

- **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**

American Association for Cancer Research

CYC065-01 Phase 1 part 2 Activity



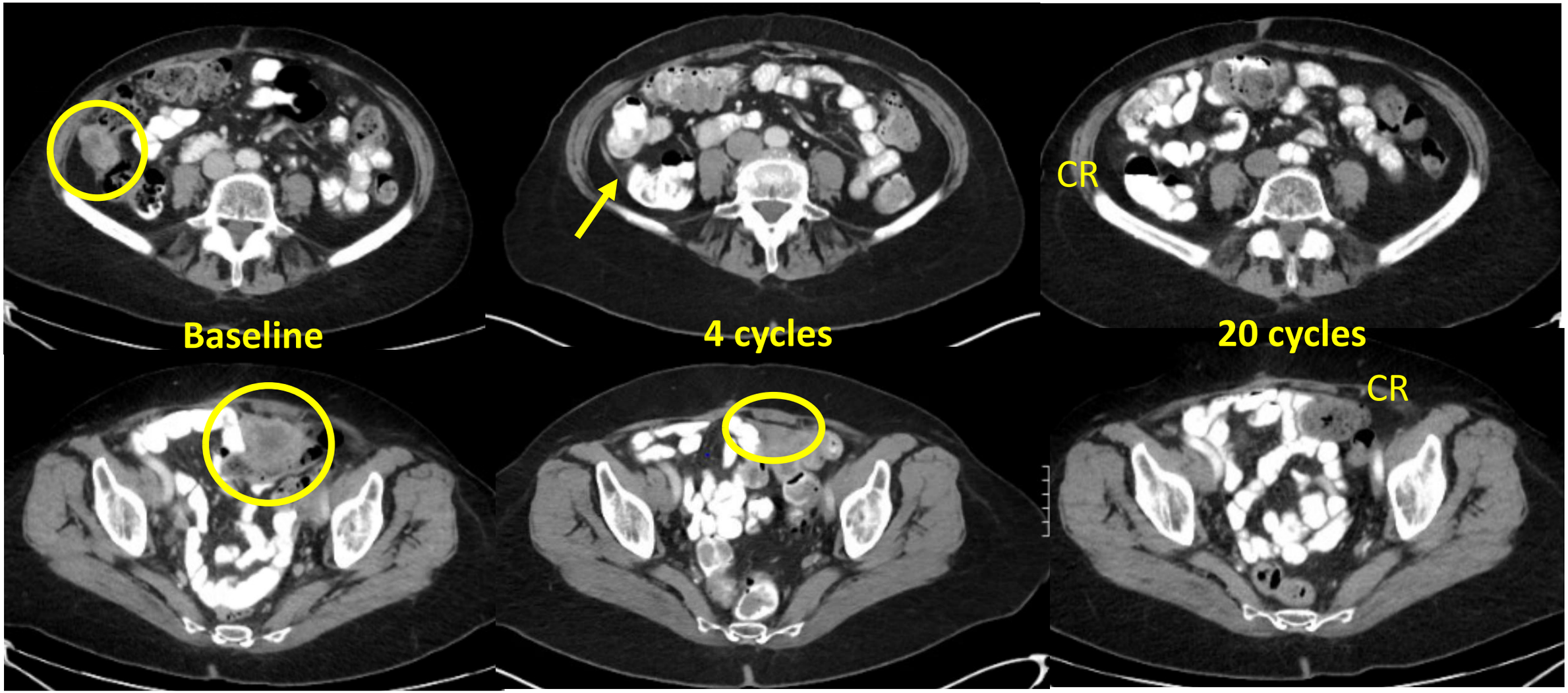
Data on file. # Non-measurable target tumor lesion.

i.v. 1h, d1, 2, 8, 9; q3wk

213 mg 1 confirmed PR and 2 SD observed

- PR at 4 cycles (MCL1 amplified endometrial; deepening response; 96% shrinkage at C27)
- SD >4 cycles (Cyclin E amplified ovarian)

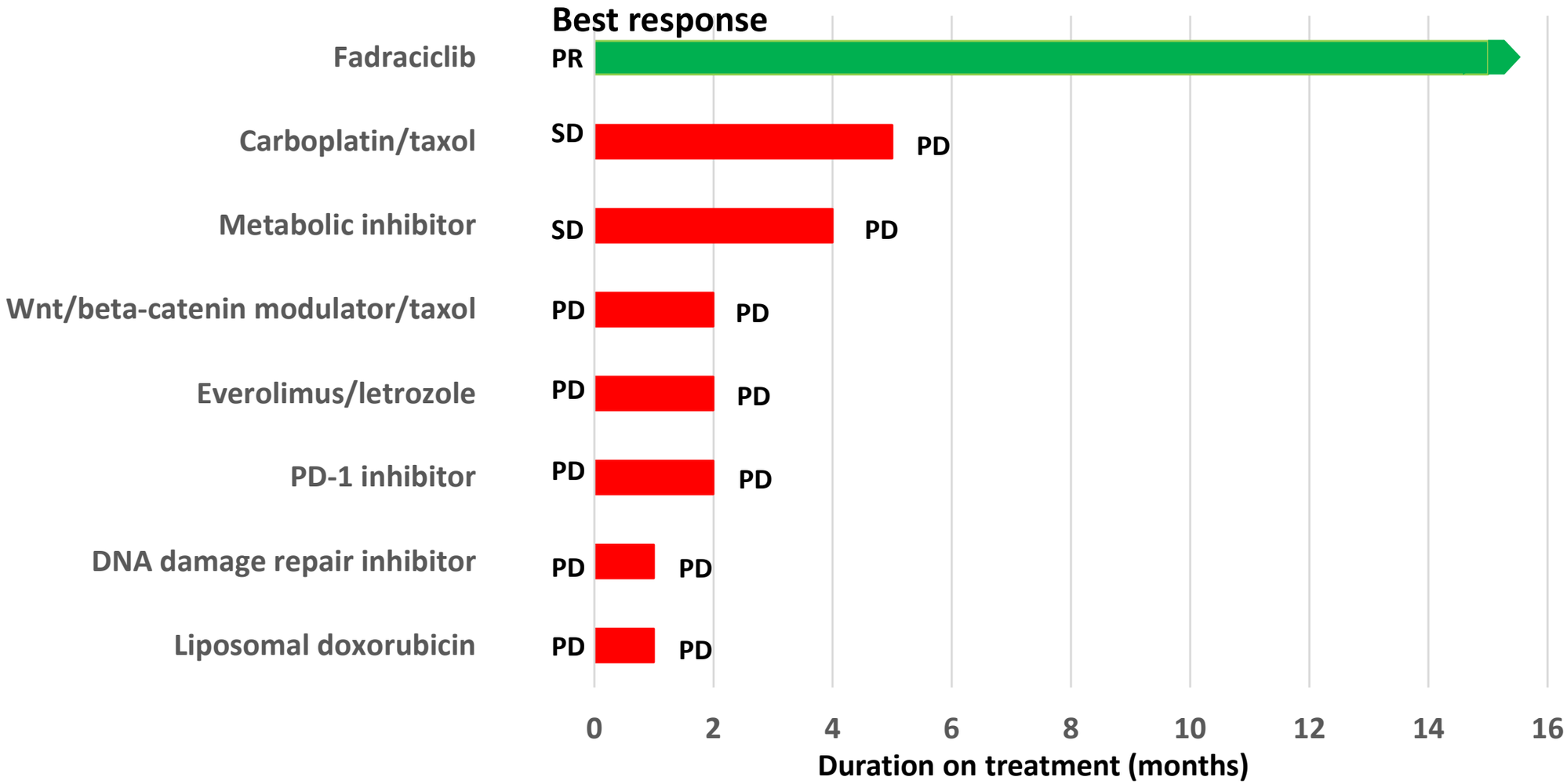
PR in MCL1 Amplified Endometrial Patient



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

Fadraciclib Most Efficacious Treatment

(endometrial adenocarcinoma patient with MCL1 amplification)



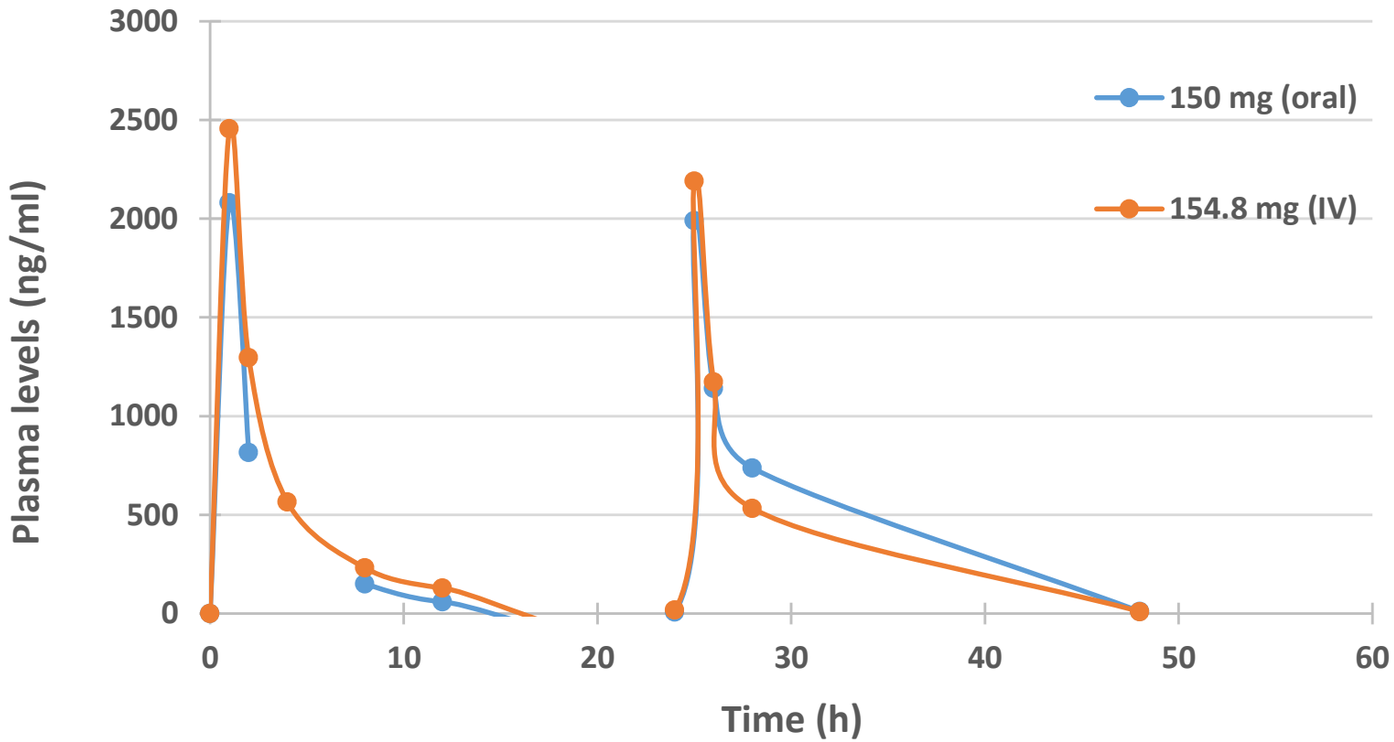
Do, KT, et al, 2nd EORTC/AACR/NCI Virtual Symposium 24-25 October 2020. PD=progressive disease.

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



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

Fadraciclib Oral Ph1/2 Solid Tumor Study Design

DOSE ESCALATION
(3+3 design; 1-3 sites)

Dose Level 3
TBD

Dose Level 2
TBD

Starting Dose Level
TBD

Dose Level -1
TBD

Schedule: 3-4 wks/cycle
Enrich for tumor types of interest to MoA.

TBD: To be disclosed.

PROOF OF CONCEPT
(Simon 2-stage; ~10 sites)

Cohort 1
Endometrial, Ovarian

Cohort 2
Breast

Cohort 3
TBD

Cohort 4
TBD

Cohort 5
TBD

Cohort 6 Basket:
TBD (expand if responses)

PIVOTAL
(if randomized study not needed; sites TBD)

Single-arm, open label, study for n=TBD cancer patients

Indication in pivotal study to be determined based on clinical data from PoC

Fadraciclib Oral Ph1/2 Leukemia Study Design

DOSE ESCALATION
(3+3 design; 1-3 sites)

Dose Level 3
TBD

Dose Level 2
TBD

Starting Dose Level
TBD

Dose Level -1
TBD

Schedule: 3-4 wks/cycle
Enrich for tumor types of interest to MoA.

TBD: To be disclosed.

PROOF OF CONCEPT
(Simon 2-stage; ~10 sites)

Cohort 1
R/R AML, older patients

Cohort 2
MDS after HMA

Cohort 3
TBD

Cohort 4
TBD

Cohort 5 Basket:
TBD (expand if responses)

PIVOTAL
(if randomized study not needed; sites TBD)

Single-arm, open label, study for n=TBD cancer patients

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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

SEER Database. Company estimates.

CDK & MCL1 Inhibitor Landscape

CDK2/9 transcriptional inhibitor enabling apoptosis and cell cycle arrest:

Fadra (CDK2/9, CYCC) Ph1 data

CDK9 transcriptional inhibitors enabling apoptosis:

VIP152 (BAY1251152; **CDK9, VINC)** Ph1 data

AZD4573 (CDK9, AZN) Ph1

CDK2 cell cycle arrest:

PF-06873600 (CDK2/4/6, Pfizer) Ph 1

MCL1 inhibitors:

AMG176 i.v. Ph 1; *murizatoclax AMG397 oral paused*; AMG176+ven *suspended*

S64315 i.v. (Servier, Ph1b +ven 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).*

Data on file; clinicaltrials.gov; Boiko S et al AACR 2019.

CYC140 PLK1 Inhibitor 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

Phase 1/2 oral development (single agent, frequent dosing, start in 2H21)

- Prespecified statistical success rules, registration enabling design
- Multiple expansion cohorts to explore activity in solid tumors, later leukemias
- Combinability with relevant MoA drugs

PLK1: Key Mitotic Regulator and Oncogene

Oncogene with key role in regulation of

— mitotic entry and exit

— spindle formation

— cytokinesis

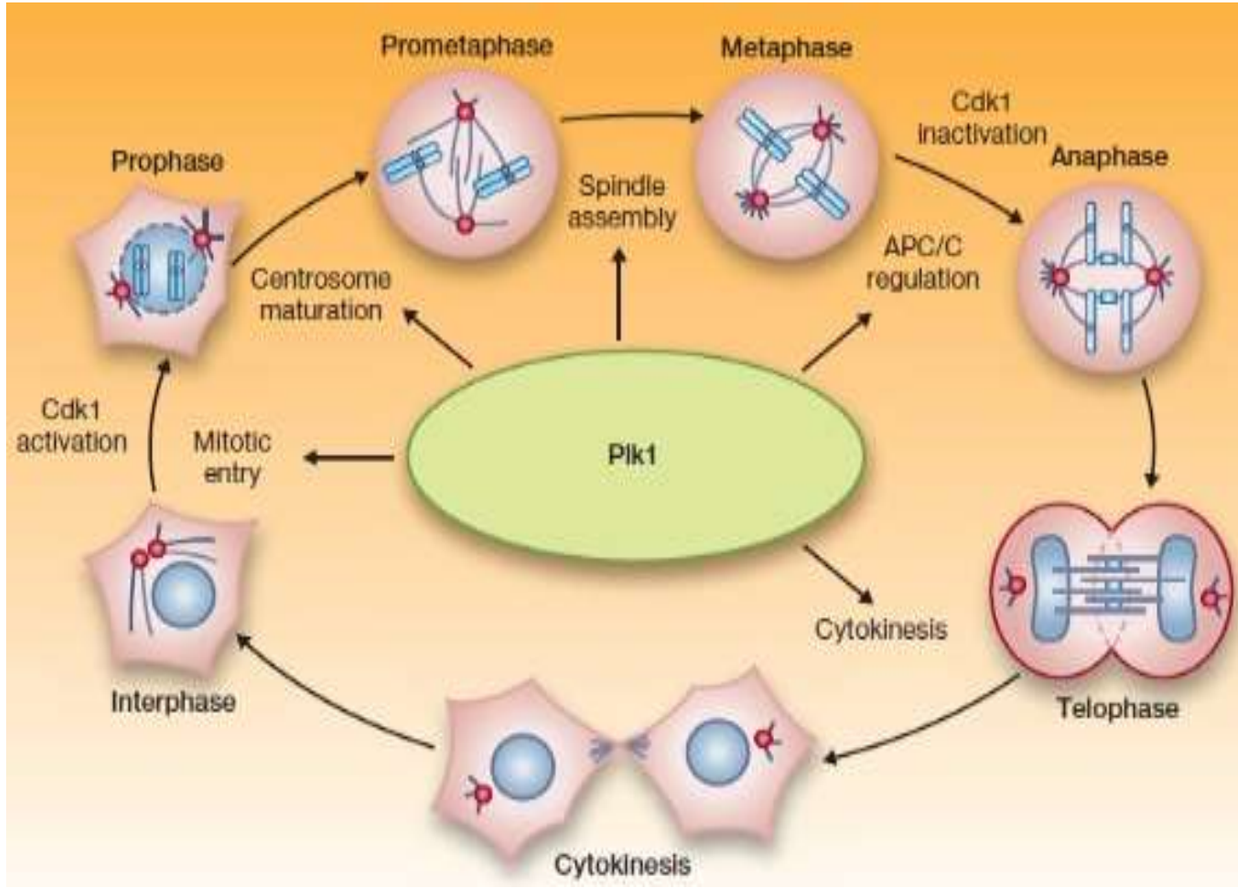
Cancer cells are very sensitive to PLK1 depletion, esp.

— mutated KRAS

— blocks proliferation by prolonged mitotic arrest

— onset of cell death in cancer cells

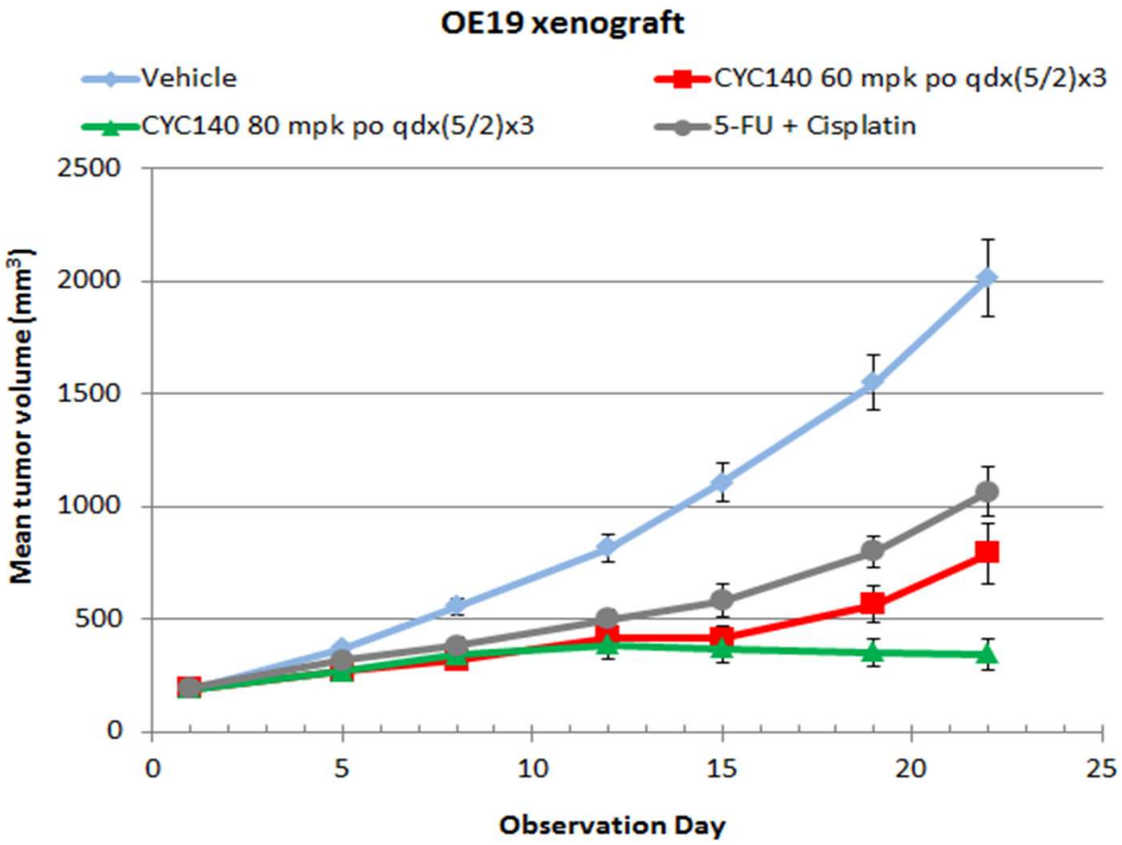
— normal cells with intact checkpoints less sensitive

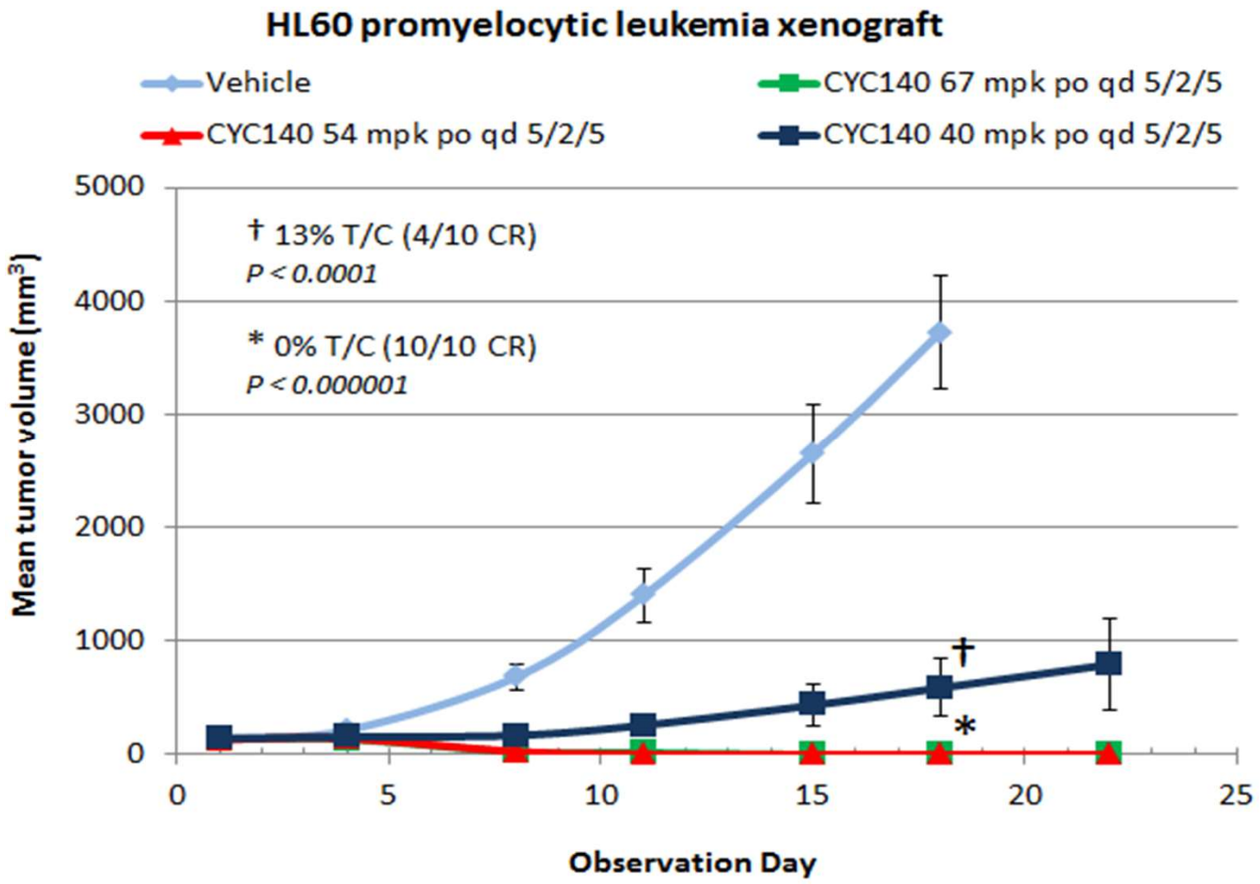


Medema RH et al. (2011) Clin Can Res 17(20):6459-66

CYC140 Preclinical Efficacy

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





Data on file.

PLK1 Inhibitor Landscape

Onvansertib oral (CRDF PLK1, CDK9, …)

Ph 1b signal in KRASmut mCRC

CYC140 (CYCC PLK1, -2, -3)

Ph 1 FIH i.v. in progress; Ph 1/2 oral to start

Discontinued:

Volasertib (BI6727 Boehringer I) Ph 3 failed

GSK 461364 (GSK) Ph 2 terminated

TAK-960 (Takeda) Ph 1 terminated

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.

PLK Inhibitors in Clinical Development

- **Volasertib *(discontinued)***
  - BTD in AML Ph2 data; but Ph3 POLO-1 in AML failed (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 1/2 in multiple solid tumors and leukemia cohorts

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.

CYC140 Oral Ph1/2 Solid Tumor Study Design

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Breast

Cohort 2
TBD

Cohort 3
TBD

Cohort 4
TBD

Cohort 5
TBD

Cohort 6 Basket:
TBD (expand if responses)

PIVOTAL
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CYC140 Oral Ph1/2 Leukemia Study Design

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Financial Position & Capitalization

Cash & cash equivalents December 31, 2020: $37.7m [1]

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

- ✔ 2018: ~ $ 6.7m [2]
- ✔ 2019: ~ $ 9.4m [2]
- ✔ 2020: ~ $ 7.9m [2]

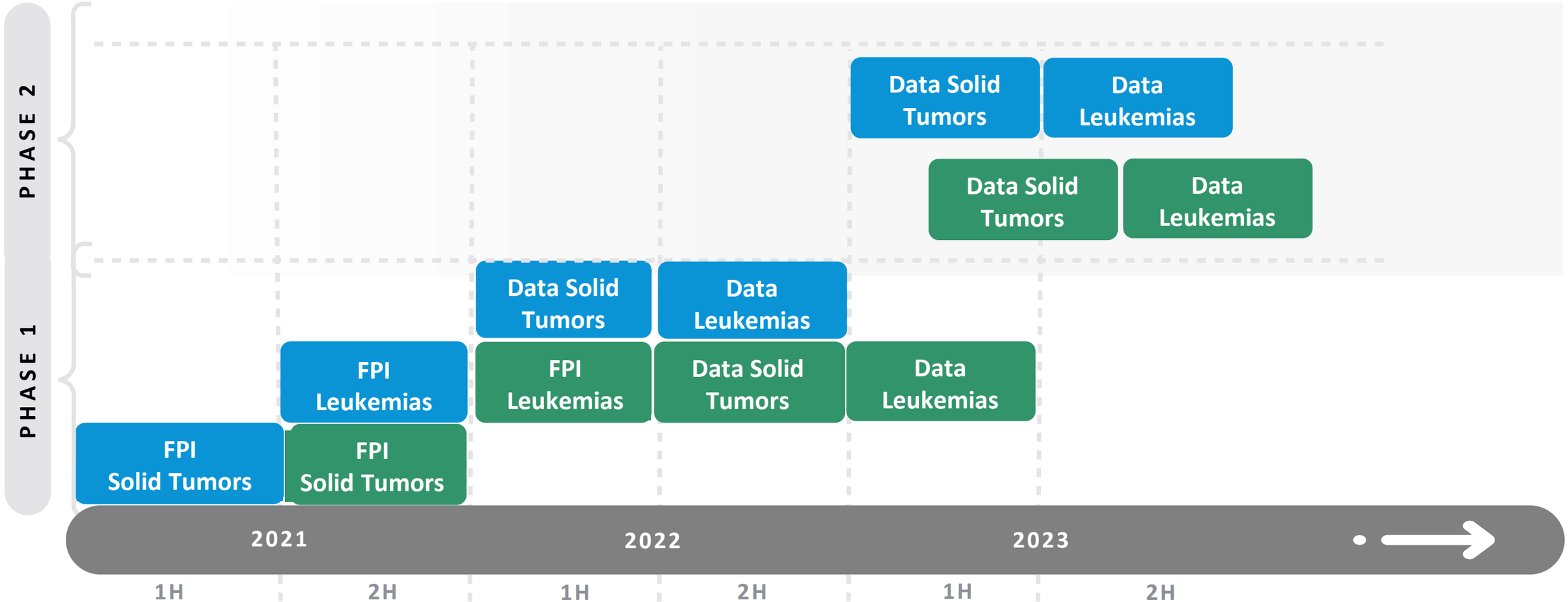
Fully diluted shares: 12.2 million[3]. No debt

Estimated capital to early 2023

1. *$33.4m (10K) + $4.3m (2021 warrant exercises); not incl. March 2021 financing.*
2. *10K*
3. *Common stock outstanding 7.1m, preferred stock 1.2m, common stock warrants 3.3m, stock options 0.6m*

Milestones

Fadra | CYC140



Cyclacel data on file. FPI = First Patient In.

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

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