CYCLACEL®

Translating cancer biology into medicines

Corporate Presentation August 2021

Disclaimer

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Cyclacel Summary

- Founded by Prof. Sir David Lane, PhD (discovery of p53): CDK2/9 hypothesis
  - Prof. David Glover, PhD (discovery of Aurora, Polo mitotic kinases): PLK-centric hypothesis
- Experienced management team
- Converting cell cycle control biology into innovative oncology medicines
- Two assets targeting CDK2/9 and PLK1 entering mid-stage development
- $47.8m cash position; recent financing brought in quality fundamental investors
- Array of multiple data readouts

Experienced Executive Leadership

Spiro Rombotis
President & CEO

Paul McBarron
COO & CFO

Mark Kirschbaum, MD
CMO

Clinical Stage Value Drivers

Fadraciclib 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 1/2 oral solid tumor study initiated in July 2021; 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 1/2 oral solid tumor study to start 2H21; multiple cohorts, registration enabling (PLK1, MYC amplified, KRAS mutated)

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Fadraciclib and CYC140 in KRAS Mutant Cancers

Fadraciclib, CDK2/9i

- Overactive colorectal cancer KRAS mutants impeded by CDK9 inhibitors[1]
- KRAS mutant pancreatic cancer sensitive to CDK9 inhibition[2]
- Fadra effective against KRAS mutant lung cancer in preclinical PDX models[3]

CYC140, PLK1i

- 140 series active in KRAS mutant colorectal cancer preclinical xenograft model[4]
- PLK1 inhibitor onvansertib + SoC: 5/14 PR in KRAS mutant colorectal patients

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[1]Lai LP, et al. SLAS Discovery 2021 [2] Blake DR, et al. Science Signalling, 2019
[3]Kawakami M, et al. Mol Cancer Ther 2021 [4]Hollick JJ, et al. AACR 2010 Abs 4435

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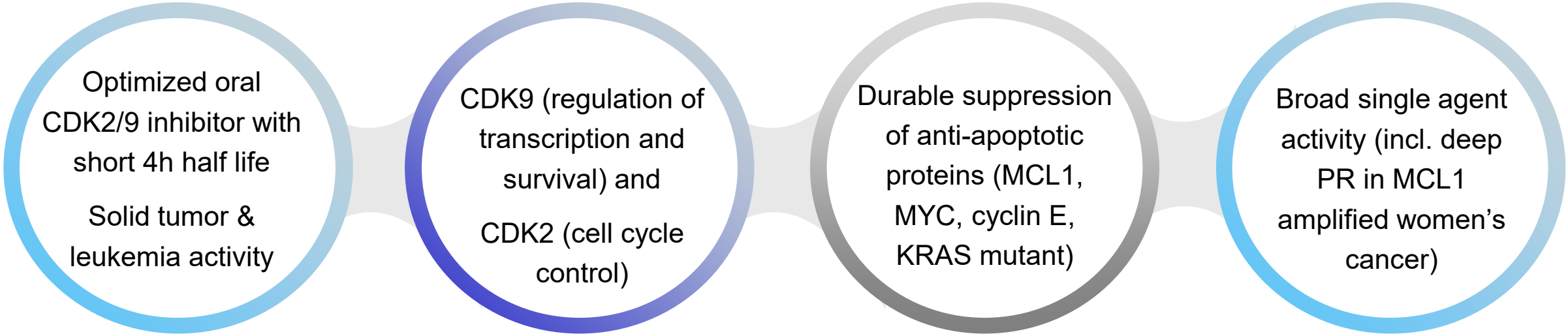
Fadraciclib (aka CYC065)

CDK2/9 inhibitor

Fadraciclib CDK Inhibitor Summary



Next step Phase 1/2 study of oral fadraciclib with optimized biological schedule in progress

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Fadraciclib CDK Inhibitor Target Profile

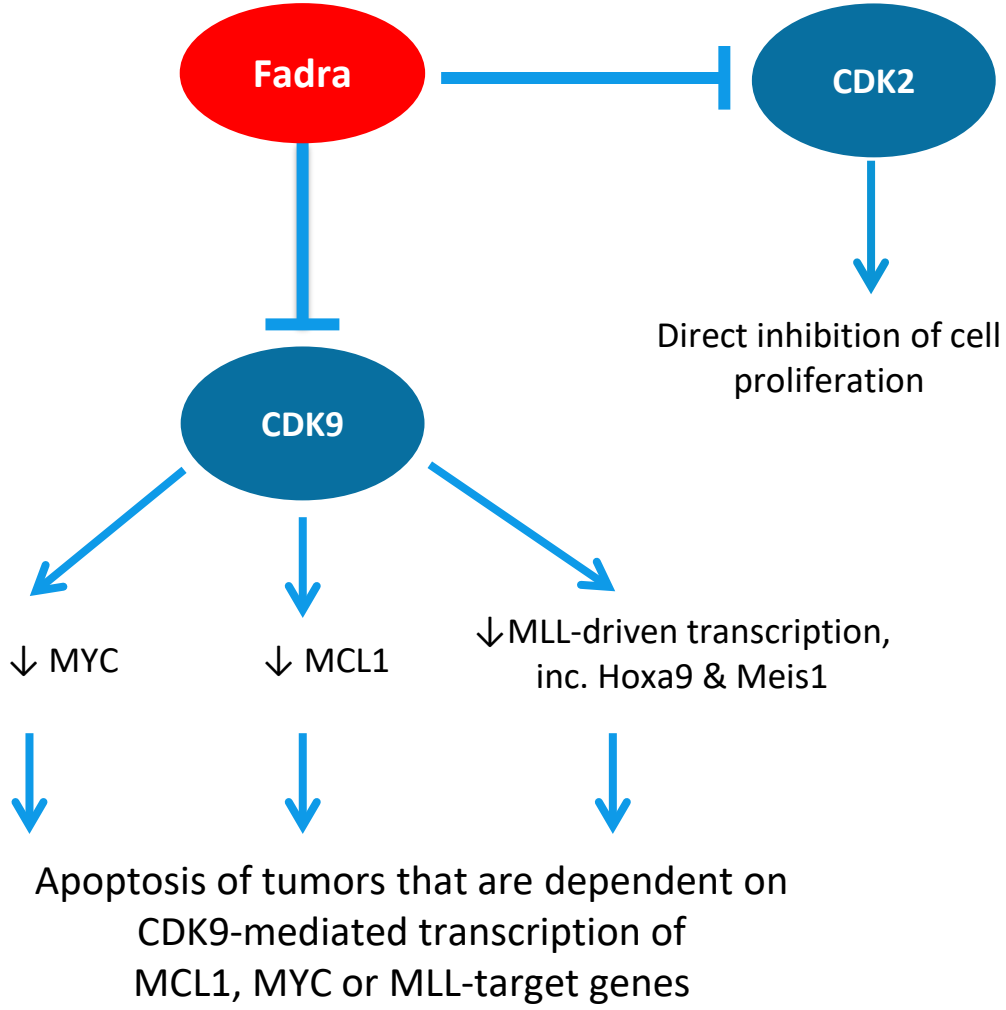
Aim: restore apoptosis (CDK2i enhances apoptosis by CDK9i) [1]

CDK9 → transcriptional regulation of anti-**apoptotic** proteins & oncogenes MCL1, MYC, MYCN, MYB, MDM2, … [1,2]

CDK2 → cell cycle checkpoint regulation (**cyclin E** (*CCNE*) overexpression leads to chemo & targeted drug resistance)

CDK4/6 inhibitor refractory, HER2+ve refractory breast CA

- *Palbociclib plus HR+ Rx failure stat sig correlated with cyclin E overexpression (PALOMA-3)* [3]
- *Cyclin E amplification/overexpression is a mechanism of trastuzumab (Herceptin®) resistance* [4]



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[1] Poon E et al, JCI 2020. [2] Frame S et al, PLOS One, 2020. [3] Turner NC et al; JCO 2019. [4] Scaltriti M et al, PNAS, 2011.

Fadraciclib Early to Mid-stage Development

Low intensity i.v. schedules (Ph 1; 1x every 3wk; 4x every 3wk)

Single agent

- Well-tolerated, short half-life, molecular target inhibition, durable PR and SD in advanced solid tumors
- Good oral bioavailability data presented at the EORTC-NCI-AACR Meeting 2020

Combination with venetoclax *(MCL1 and BCL2 double-hit strategy)*

- R/R AML: Reduction in peripheral blast counts, TLS observed at highest dose
- R/R CLL: Lymph node reduction, MRD +ve to MRD –ve conversion observed

Next step Ph 1/2 studies with oral, optimized biological schedule

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MRD: Minimal Residual Disease; TLS: Tumor Lysis Syndrome

Phase 1 First-in-Human Study in Solid Tumors

Primary objective

Determine fadraciclib MTD and recommended Phase 2 dose (RP2D)

Secondary objective

Evaluate pharmacokinetics

Assess PD markers (RNA Pol II CTD P-Ser2 and MCL1 levels in PBMCs)

CYC065-01 design (single agent)

Open label, single arm, dose escalation study in patients with advanced solid tumors. 3-part study:

- Part 1: 4h infusion 1x every 3wk; n=26
- Part 2: 1h infusion 4x every 3wk (d1, d2, d8, d9); n=26
- Part 3: oral 4x every 3wk (d1, d2, d8, d9); n=7

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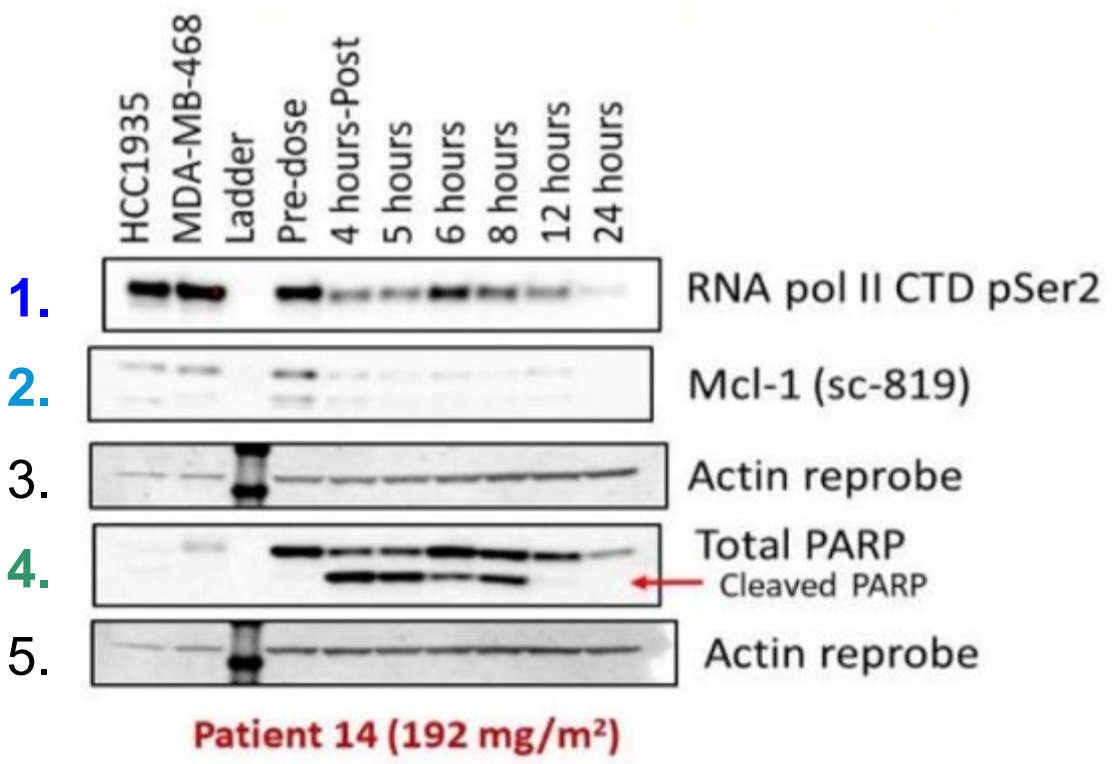
Fadraciclib's Target Inhibition Facilitates Cancer Cell Apoptosis

Target inhibition detectable at 24 hours



American Association for Cancer Research

Markers of interest: Western Blot analysis

Row 1: Reduction of RNA Polymerase II C-terminal domain Serine 2 phosphorylation (inhibition of CDK9)

Row 2: Suppression of MCL1 level in patient sample within 4h of starting treatment; MCL1 levels remained suppressed up to 24h

Row 4: Cleaved PARP enzyme during fadraciclib treatment in patients indicating engagement of apoptosis

Rows 3 and 5: Control protein for normalization

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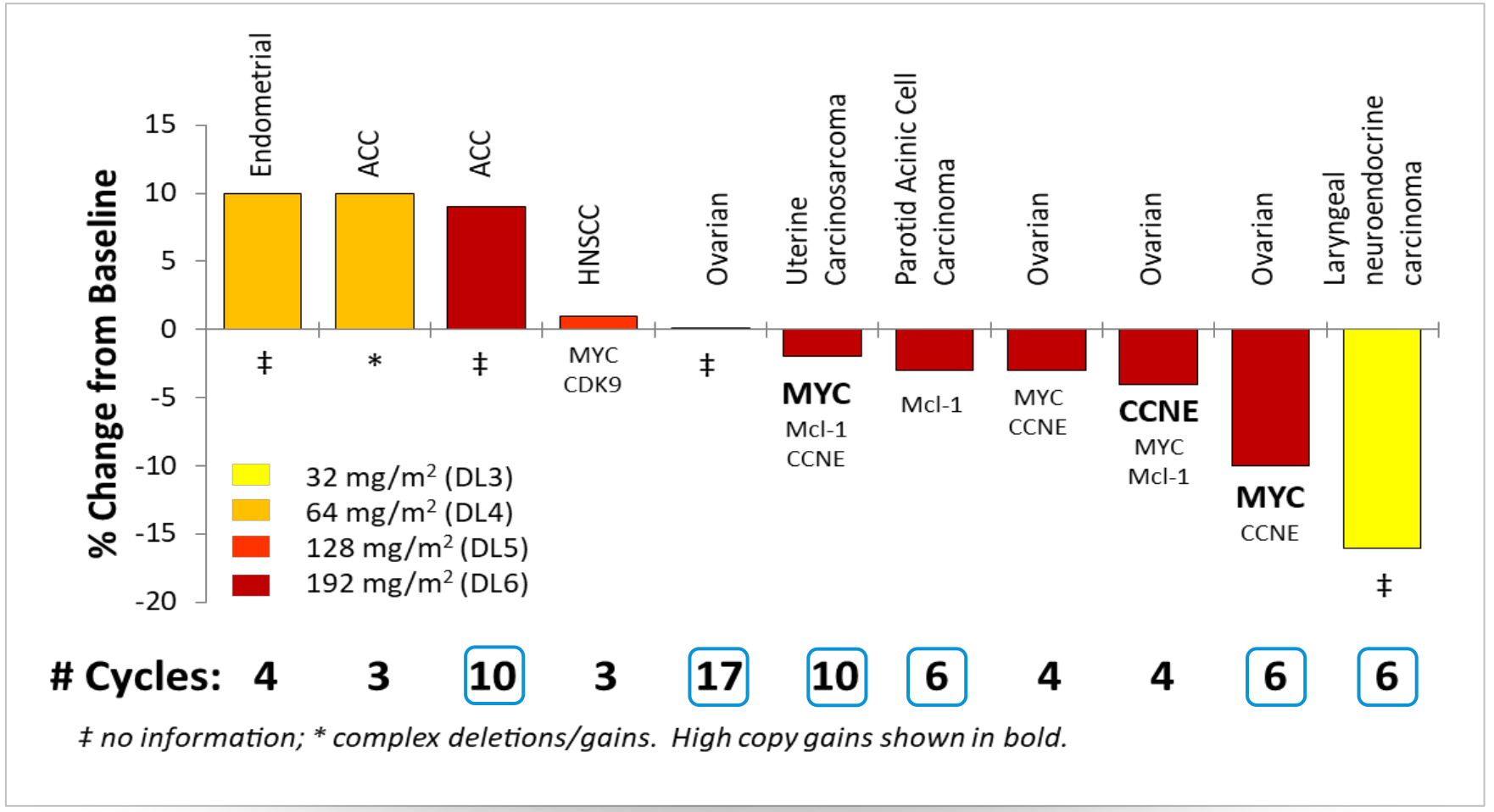
Do, Khanh T., et al., AACR Annual Meeting 2018. RP2D = 192mg/m²

CYC065-01 Phase 1 Part 1 Change in Tumor Volume



AACR American Association for Cancer Research

Patients with high copy CCNE, MYC and/or MCL1 sensitive to single-agent fadraciclib

4h infusion every 3wk:

- 20/26 patients evaluable (RECIST 1.1 response)
- 6/11 achieved SD for 6 or more cycles (*boxed*)

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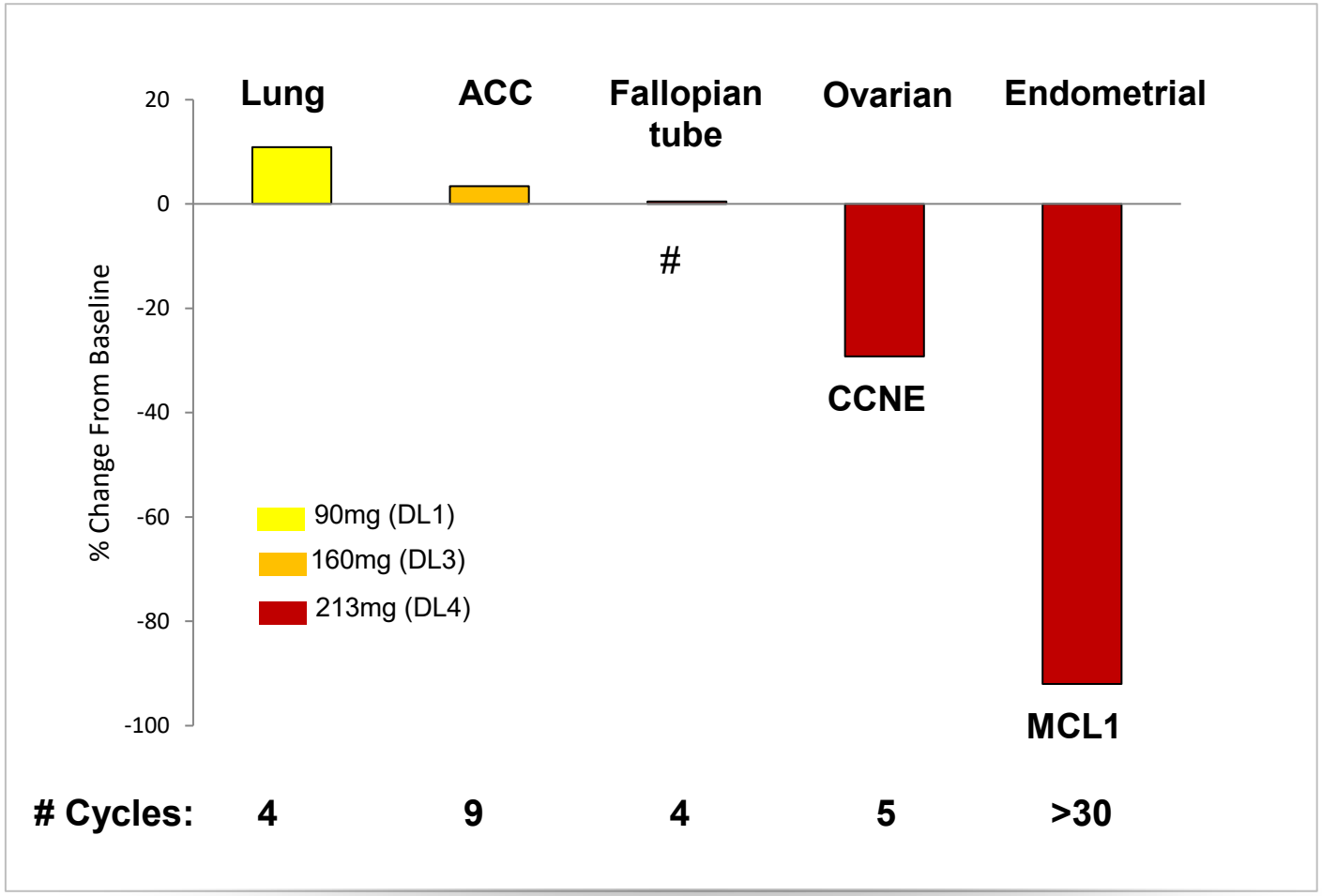
Do, Khanh T., et al., AACR Annual Meeting 2018.

CYC065-01 Phase 1 Part 2 Activity



Tumors with MCL1 and CCNE overexpression respond to fadraciclib single agent

- Improved efficacy with more frequent 1h infusions on d1, 2, 8, 9 every 3wk
- Confirmed PR at 4 cycles (MCL1 amplified endometrial cancer; deep ongoing response ~2 years; 100% shrinkage at cycle 33)
- SD >4 cycles in cyclin E amplified ovarian cancer

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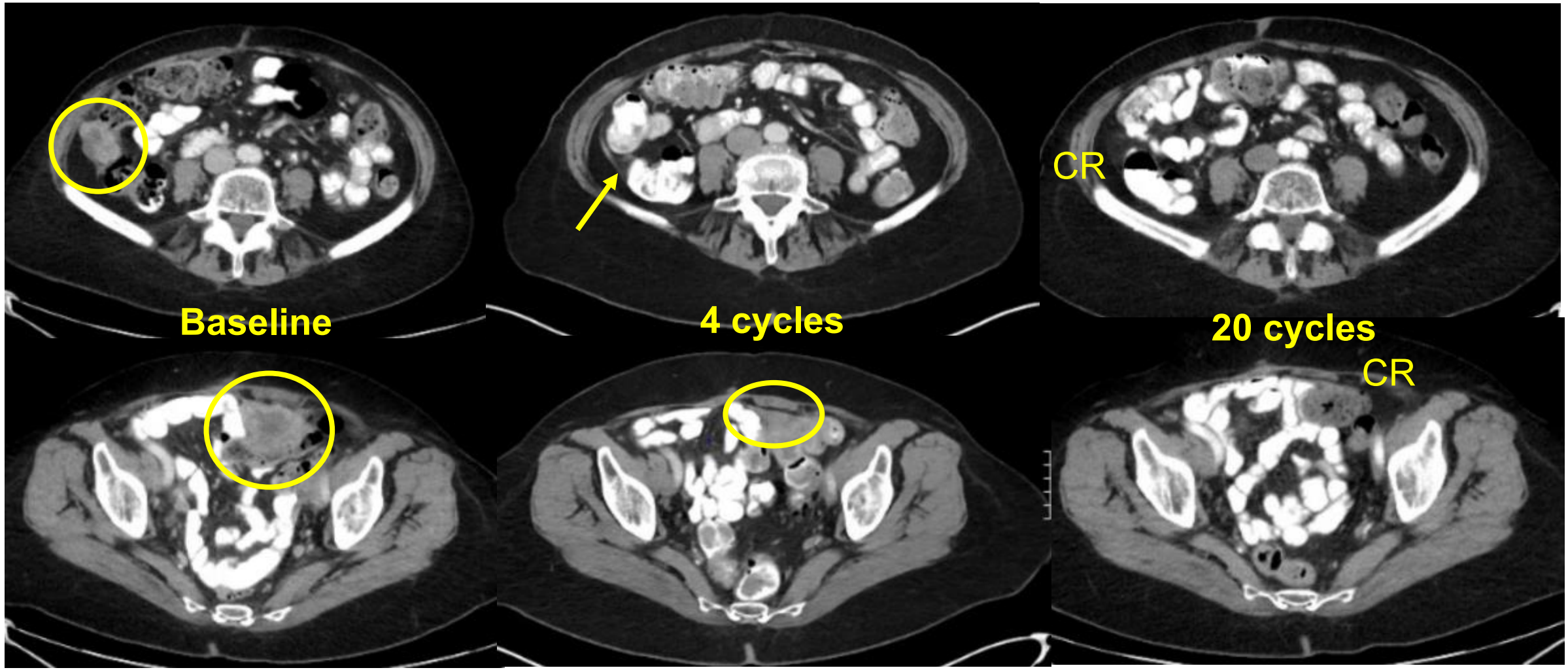
Data on file. # Non-measurable target tumor lesion.

PR in MCL1 Amplified Endometrial Patient



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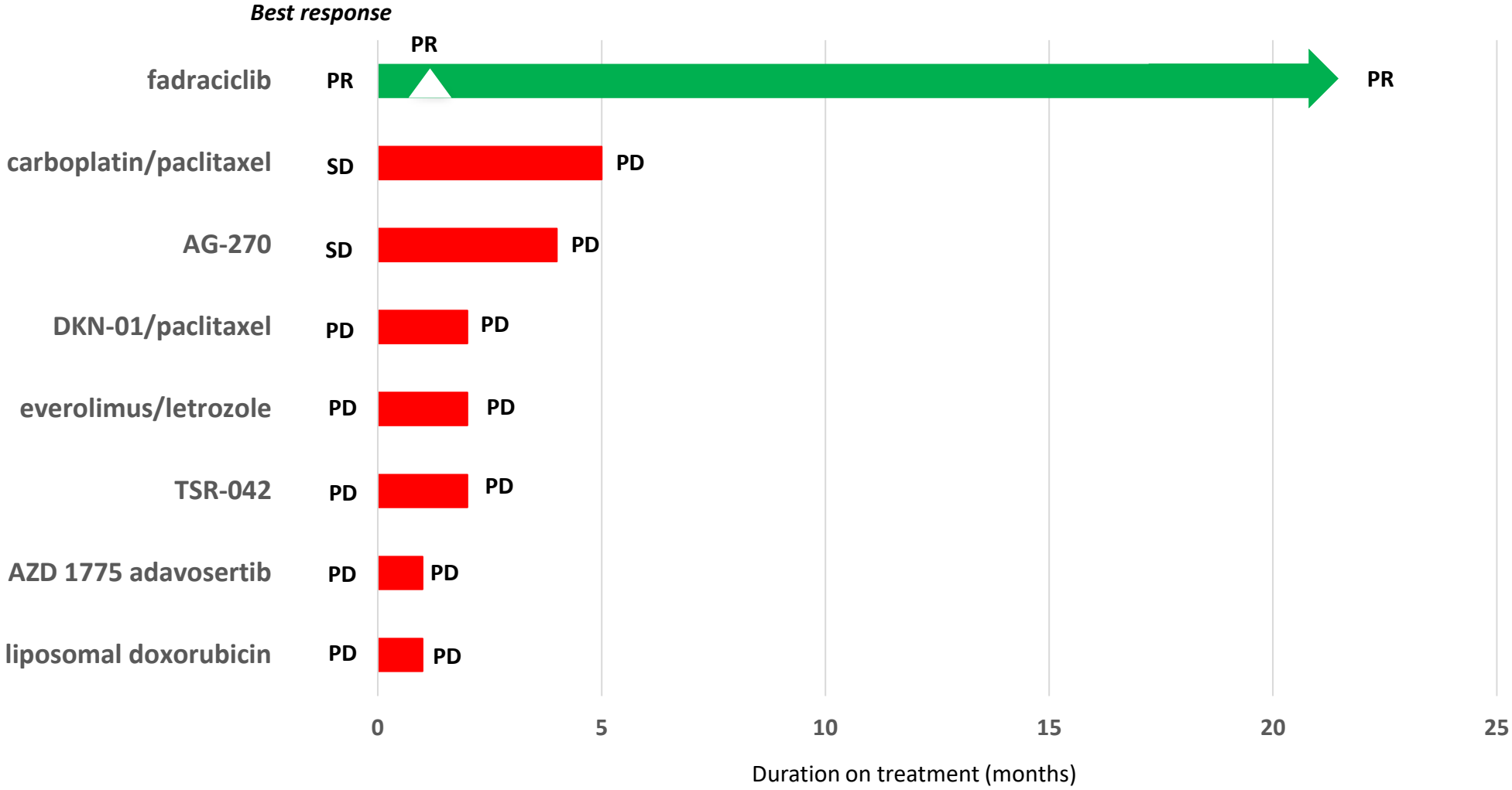
Do, KT, et al, 2nd EORTC/AACR/NCI Virtual Symposium 24-25 October 2020.

Fadraciclib Most Efficacious Treatment

(endometrial adenocarcinoma patient with MCL1 amplification)



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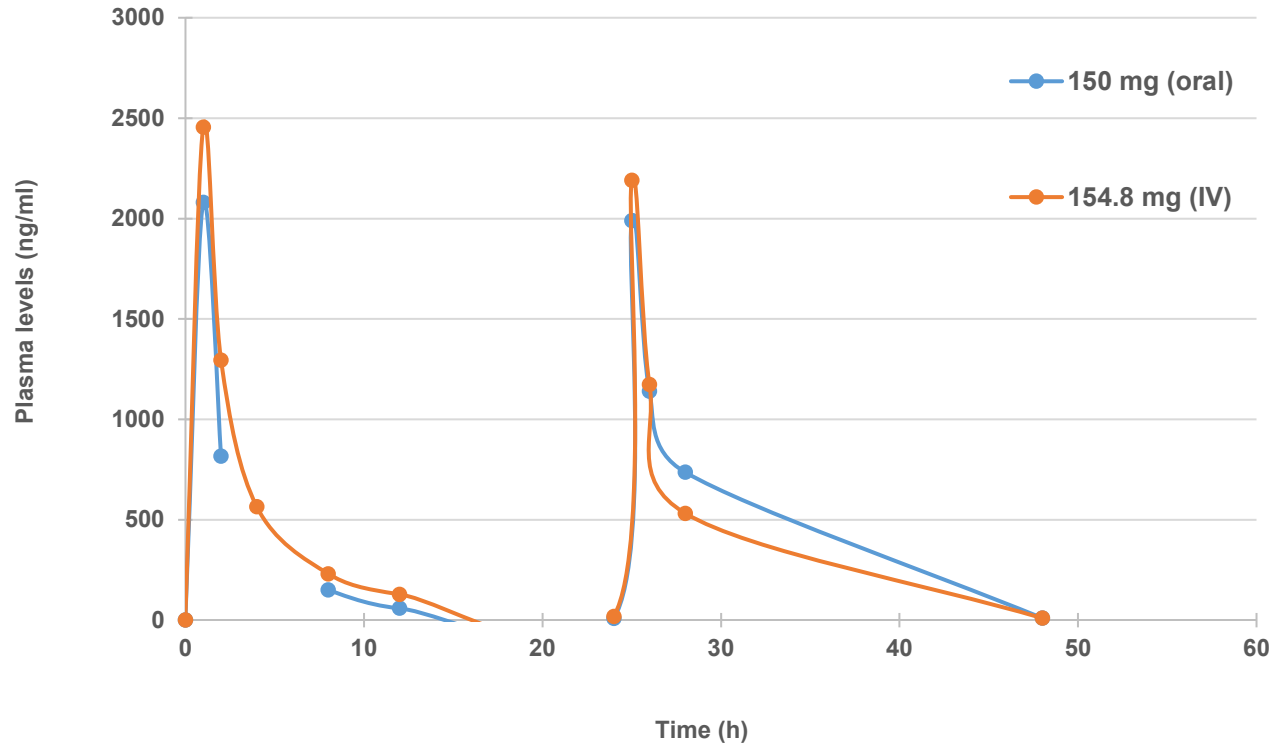
Do, KT, et al., 32nd EORTC/AACR/NCI Virtual Symposium 24-25 Oct. 2020. PD=progressive disease. SD=stable disease.

CYC065-01 Phase 1 Part 3 Oral Bioavailability

Oral dosing regimen: qd on days 1, 2, 8 and 9 every 3 wk; 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 Phase 1/2 Solid Tumor Study Design

Dose Escalation*
(3+3 design; 1-3 sites)

Dose Level 4
100mg bid daily M to F

Dose Level 3
75mg bid daily M to F

Dose Level 2
50mg bid daily M to F

Starting Dose Level
50mg bid daily MWF

Dose Level -1
50mg bid M Th

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

Proof of Concept*
(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, 6
Lymphoma (B-cell; T-cell)

Cohort 7
mCRC (including KRAS mutated)

Cohort 8 Basket: tumors suspected to have related MoA (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

First patient dosed in DE part in July 2021; ClinicalTrials.gov Identifier: NCT04983810.

*Single agent **Single agent; followed by combination TBD: To be disclosed.

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Fadraciclib Oral Phase 1/2 Leukemia Study Design

Dose Escalation*
(3+3 design; 1-3 sites)

Dose Level 4
100mg bid daily M to F

Dose Level 3
75mg bid daily M to F

Dose Level 2
50mg bid daily M to F

Starting Dose Level
50mg bid daily MWF

Dose Level -1
50mg bid M Th

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

Proof of Concept*
(Simon 2-stage; ~10 sites)

Cohort 1
R/R AML/MDS, older

Cohort 2
CLL

Cohort 3;4
AML combo +aza; +ven

Cohort 5
CLL combo +ven

Cohort 6 Basket: tumors suspected to have related MoA (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

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**Single agent **Single agent; followed by combination TBD: To be disclosed.*

Fadraciclib is Addressing Large Markets (e.g. cyclin E / CCNE1)

High Grade Serous Ovarian Cancer 2L

- 27k US incidence; ~79k prevalence
- CCNE1 amplified >20% of patients; worse survival than BRCA mutant patients

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

CYCLACEL® *SEER Database. Company estimates.*

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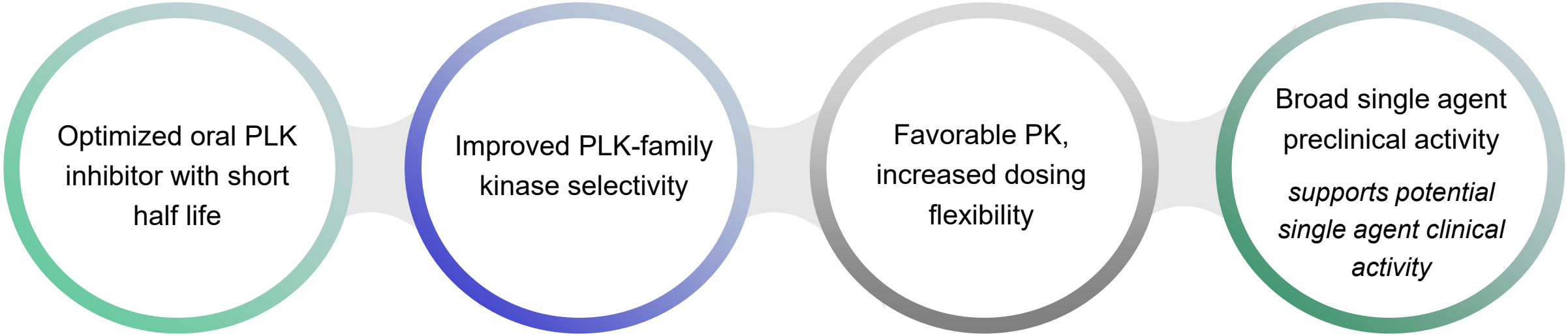
CYC140

PLK1 Inhibitor

CYC140 PLK1 Inhibitor Summary



Next step Phase 1/2 oral CYC140 with optimized biological schedule

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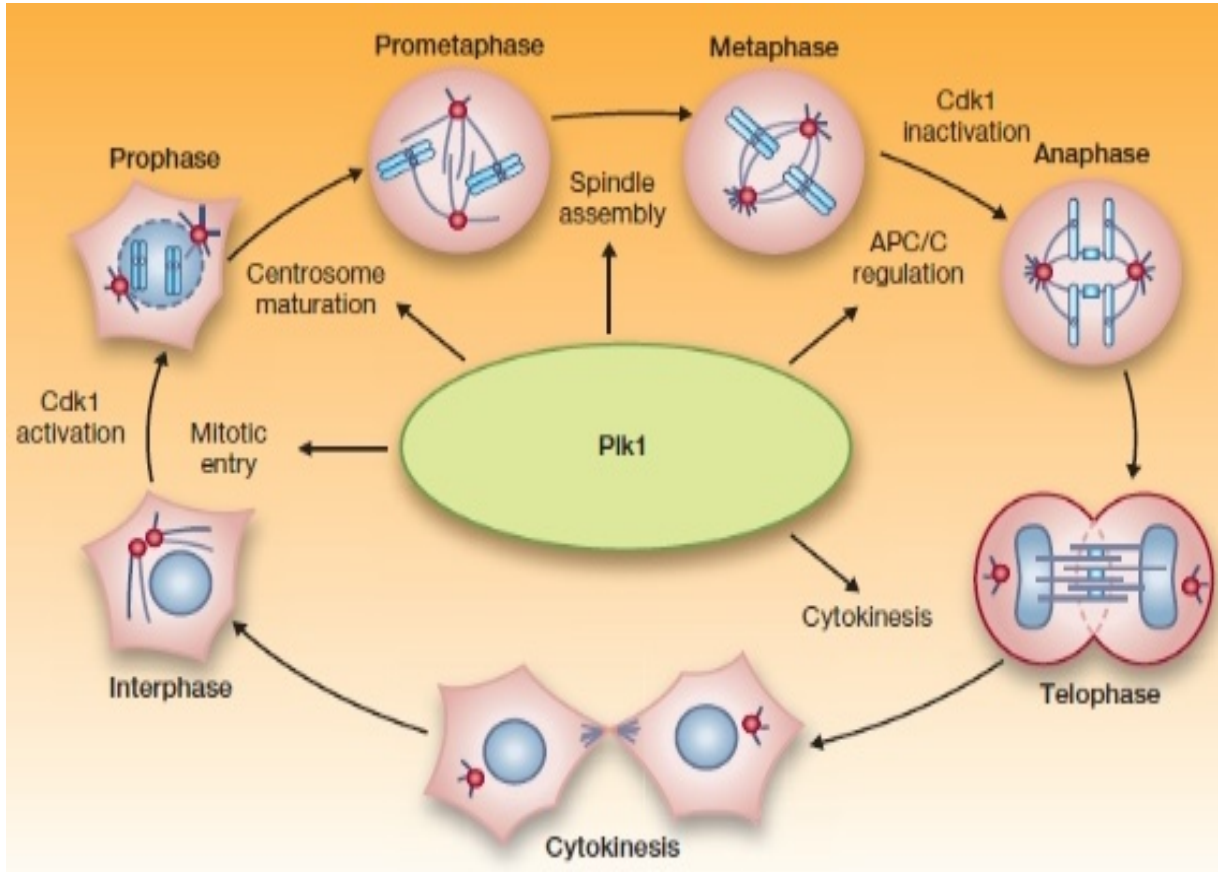
PLK1: Key Mitotic Regulator

Oncogene with key role in regulation of

- mitotic entry and exit
- spindle formation
- cytokinesis

Cancer very sensitive to PLK1 depletion, esp.

- mutated KRAS and p53(-)
- blocks proliferation by prolonged mitotic arrest
- onset of apoptotic death in cancer cells
- normal cells with intact checkpoints less sensitive



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

PLK Inhibitors in Clinical Development

Volasertib

(Boehringer Ingelheim; i.v. BI-6727 discontinued)

- BTD in AML Ph2 data; but Ph 3 POLO-1 in AML failed (imbalance of deaths)
- Dose intensity led to single agent activity; long terminal half-life ~110h

Onvansertib

(Cardiff; p.o., 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; mPDAC with chemo

CYC140

(Cyclacel; p.o. and i.v. selectivity mainly PLK1, secondarily PLK2, PLK3)

- Preclinical activity in multiple solid tumors and leukemias; terminal $t_{1/2}$ ~11h
- Aim: oral, dose intense, Ph 1/2 in multiple solid tumors and leukemia cohorts
- Rapid read-out of single agent clinical activity followed by registration-enabling single agent and/or combination designs

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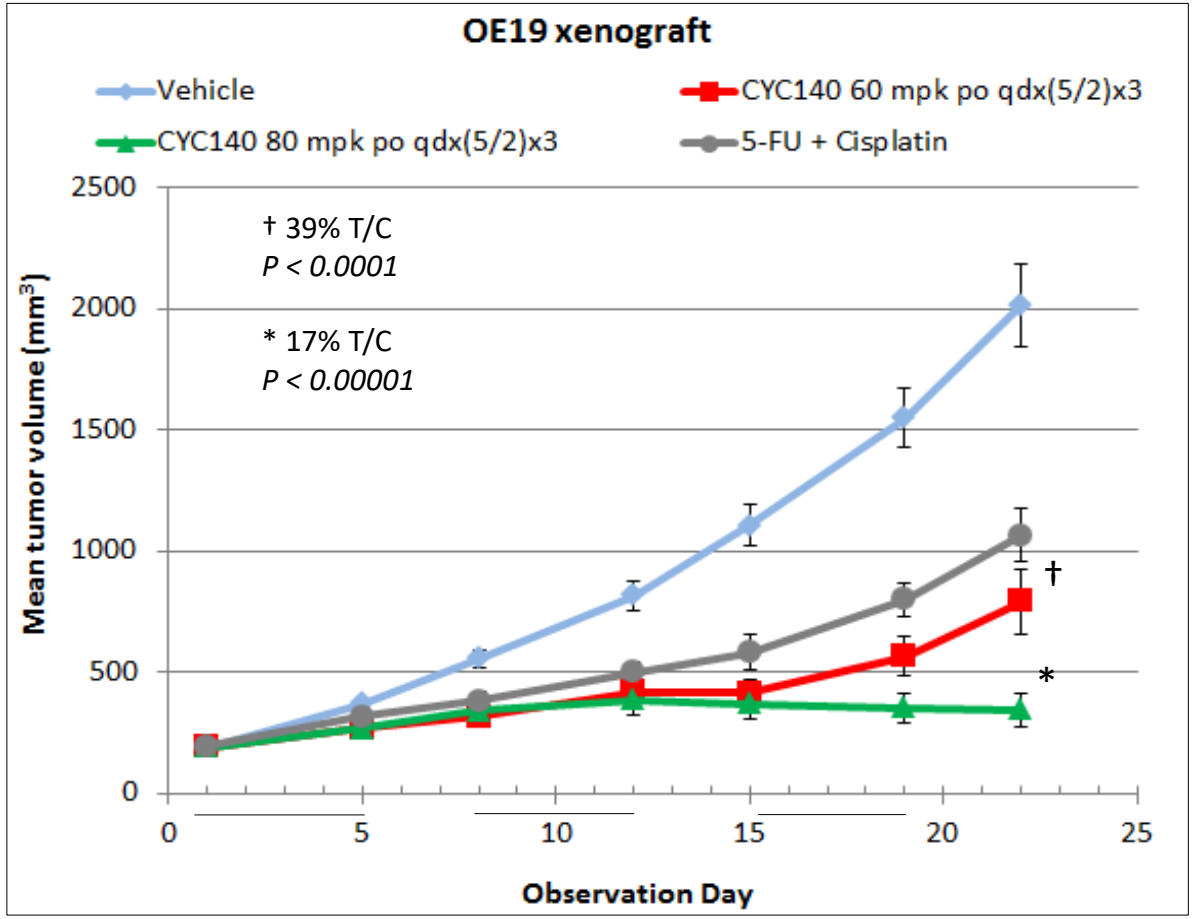
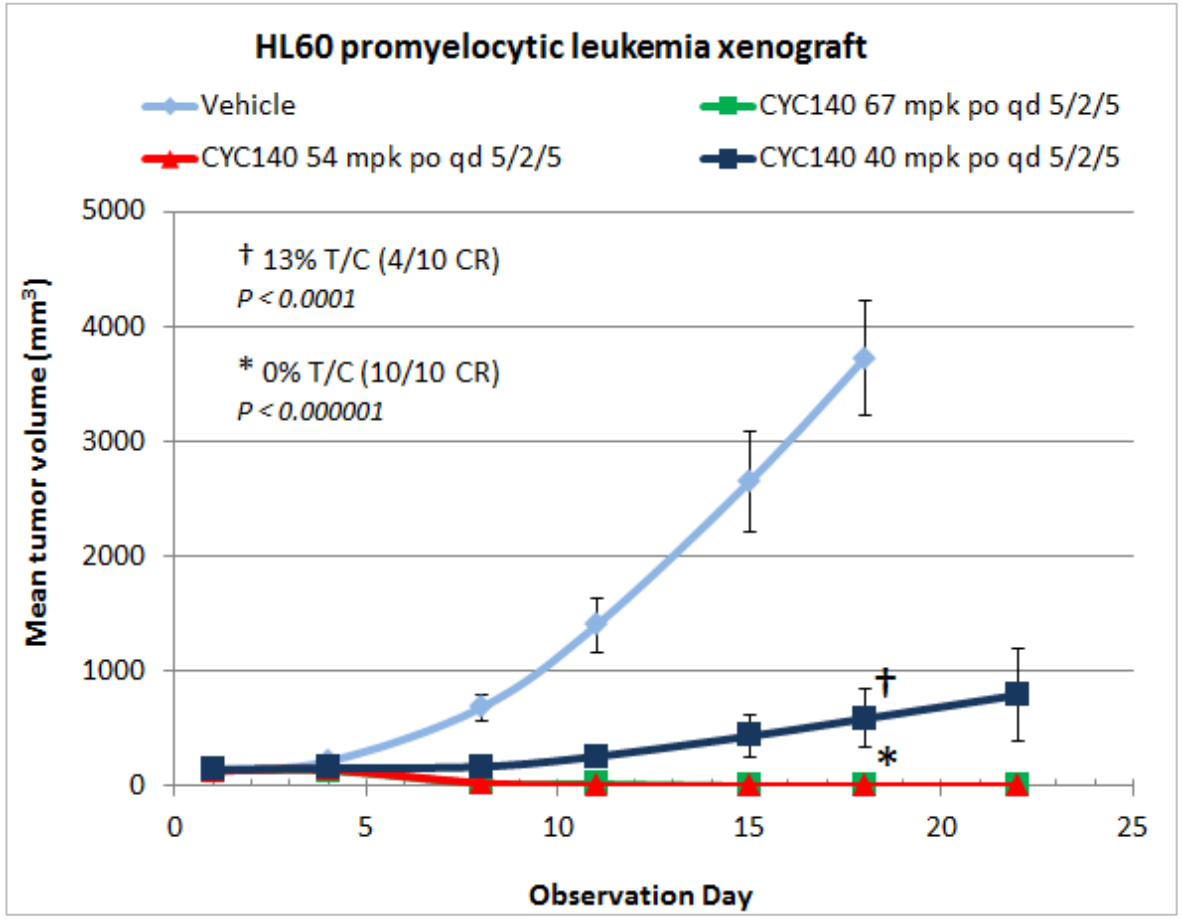
*Data on file. *Valsasina B et al Mol Can Ther 2012 11 1006; https://mct.aacrjournals.org/content/11/4/1006.figures-only.*

CYC140 Preclinical Efficacy

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





CYC140 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 wk/cycle. Enrich for tumor types of interest to MoA

Proof of Concept*
(Simon 2-stage; ~10 sites)

Cohort 1
mCRC (incl. KRAS mut)

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

CYCLACEL® *Single agent **Single agent; followed by combination TBD: To be disclosed.

CYC140 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 wk/cycle. Enrich for tumor types of interest to MoA

Proof of Concept*
(Simon 2-stage; ~10 sites)

Cohort 1
R/R AML, older patients

Cohort 2
MDS after HMA

Cohort 3
AML combo

Cohort 4
CLL combo

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

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

CYCLACEL® *Single agent **Single agent; followed by combination TBD: To be disclosed.

Financial Position & Capitalization

Pro forma cash & cash equivalents $47.8 millilon[1] as of March 31, 2021

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

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

Fully diluted shares: 14.3 million[3]; no debt

Estimated capital to early 2023

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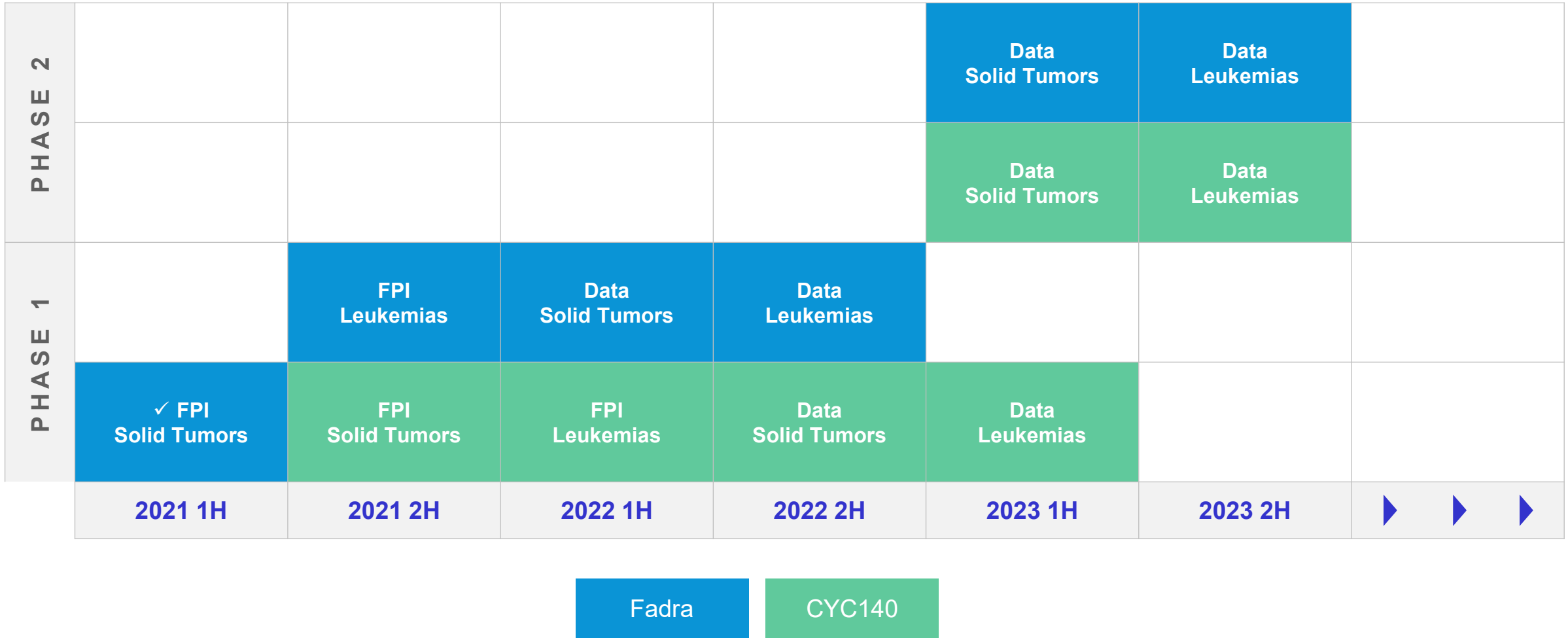
[1.] 10Q . [2] 10K. [3].Common stock outstanding 9.2m, preferred stock 1.2m, common stock warrants 3.2m, options 0.7m

Expected Milestones



Cyclacel data on file. FPI = First Patient In.

Investment Thesis

- Clinical stage, state-of the-art oncology programs
- Targeting molecularly-defined patient populations
- CDK inhibitors: validated drug class; PLK inhibitors: emerging drug class
- Competitively positioned
- Significant market opportunities

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Thank You

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