Translating cancer biology into medicines

Cyclacel Pharmaceuticals, Inc. (CYCC) JUNE 2024

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Cyclacel Opportunity

Discovered and developing **fadraciclib** & **plogosertib** cell cycle, drug portfolio

Fadra potentially **best-in-class**, next generation CDK inhibitor

Unique Ph 2 precision medicine strategy: patients with CDKN2A/CDKN2B mutations

Single-agent anticancer activity (CR, PR, SD) with good tolerability including:

- GYN (incl. breast/endometrial/ovarian), hepatobiliary, NSCLC, pancreatic, testicular and lymphoma

Enroll two Phase 2 cohorts with readouts in Q4 ’24 – Q1 ’25; potentially supporting registration pathways

Fadra Patient Groups

- Two dose escalation studies:
  - 065-01 IV (n=52)
    - 20/52 had sequencing data
    - 6/20 had CDKN2A and/or CDKN2B alterations
  - 065-101 oral (n=47)
    - 21/47 had sequencing data
    - 5/21 had CDKN2A and/or CDKN2B alterations

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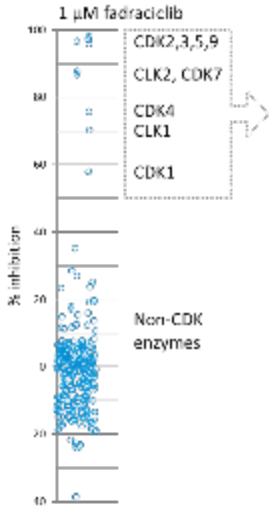
Data on file.

Responder Profiles: CDKN2A/B Alterations *(retrospective review)*

Patient *Study*	Histology	Best Response (sum of target lesions)	Dose Level	Schedule	Mutation
38 iv *065-01*	Endometrial	**CR** (-100%)	213mg QD	2d/wk 2/3 wks	CDKN2A, CDKN2B, MTAP loss, MCL1 amp
14 iv *065-01*	Ovarian	**SD** (-2.5%)	192mg/m^2	1d/3 wks	CDKN2A, CCNE1, MYC gain
11 iv *065-01*	Salivary gland	**SD** (0.8%)	128mg/m^2	1d/3 wks	CDKN2A mutation & gain CDKN2B gain
51 oral *065-101*	NSCLC squamous	**SD** (-22%)	125mg BID	5d/wk 4/4 wks	CDKN2B loss
21 oral *065-101*	PTCL angioimmunoblastic	**PR** (-16%)	100mg BID	5d/wk 4/4 wks	CDKN2A mutation
16 oral *065-101*	Cholangiocarcinoma	**SD** (-5%)	75mg BID	5d/wk 4/4 wks	CDKN2A mutation
55 oral *065-101*	Pancreatic	**SD** (4%)	125mg BID	5d/wk 4/4 wks	CDKN2A loss
62 oral *065-101*	Sertoli germ cell testicular	**SD** (-12%)	150mg QD	7d/wk 4/4 wks	CDKN2A, CDKN2B, MTAP loss

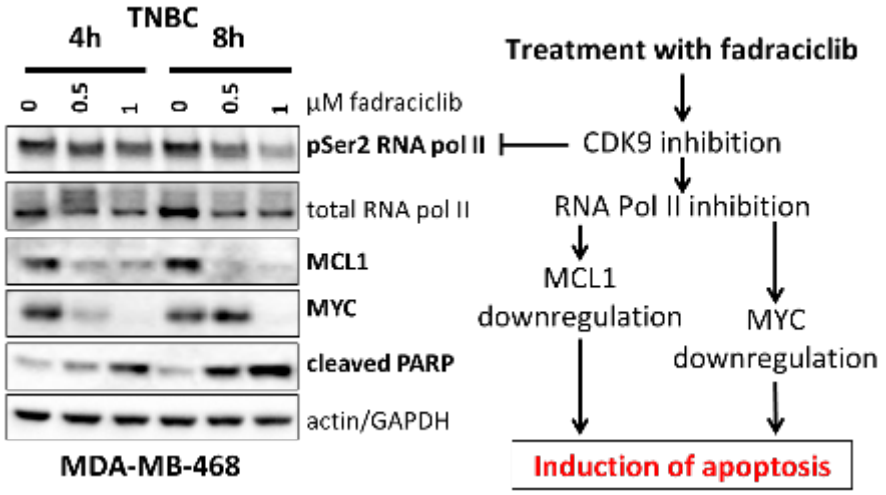
Fadra – Novel and Potent CDK2 and CDK9 inhibitor

Kinase Profile

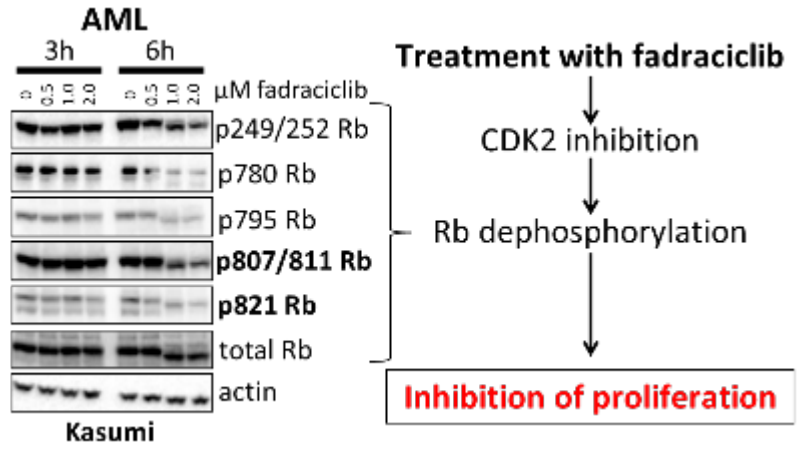


Enzyme	Fadraciclib IC_{50} (nM)	Fold Diff. to CDK2
CDK2	**4.5**	**1.0**
CDK5	**20.5**	**4.6**
CDK9	**26.2**	**5.8**
CDK3	**28.9**	**6.4**
CDK7	193	43
CDK4	232	52
CLK2	252	56
CLK1	549	122
CDK1	578	128

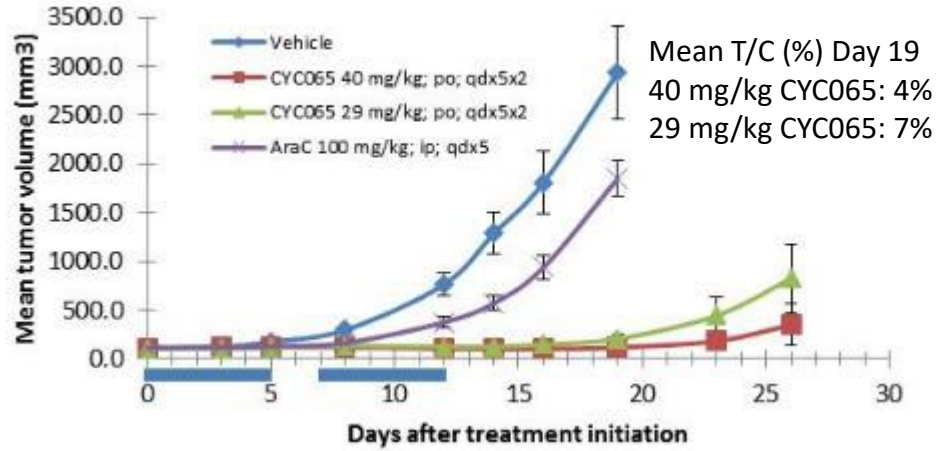
CDK9 inhibition



CDK2 inhibition

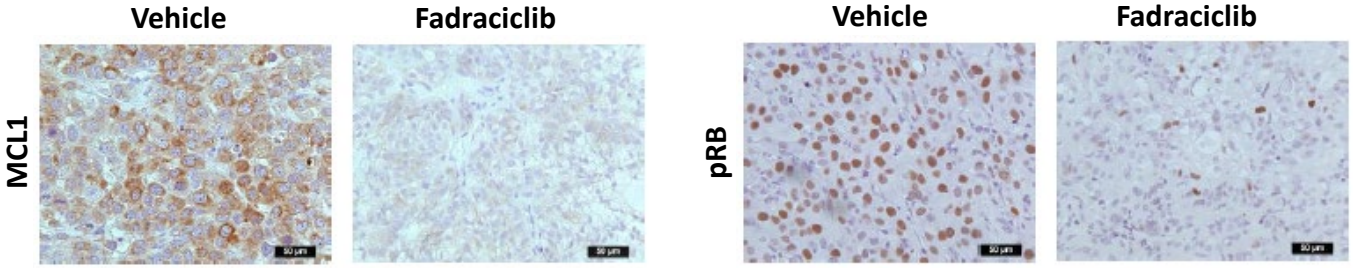


EOL-1 (KTM2A-PTD, CDKN2A/B Loss) AML xenograft



Mean T/C (%) Day 19
40 mg/kg CYC065: 4%
29 mg/kg CYC065: 7%

Depletion of MCL1 level and Rb phosphorylation (pRB) *in vivo* following fadraciclib treatment of lung cancer PDX models



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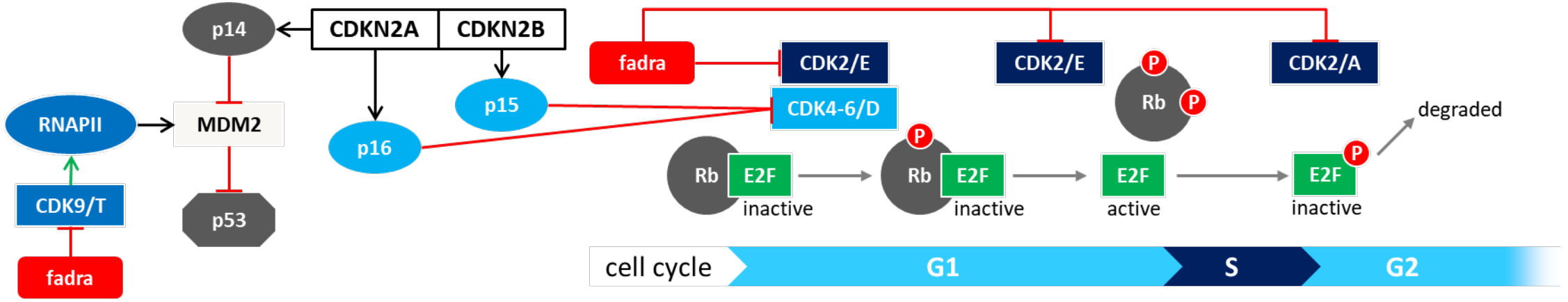
Frame, PLoS One 2020, 15:e0234103; Kawakami, Mol Cancer Ther 2021, 20:477

CDKN2A/B and Fadra MoA



CDKN2A encodes p16^{INK4a}, *CDKN2B* p15^{INK4b} which inhibit D-type cyclin complexes w/ CDK4 & CDK6

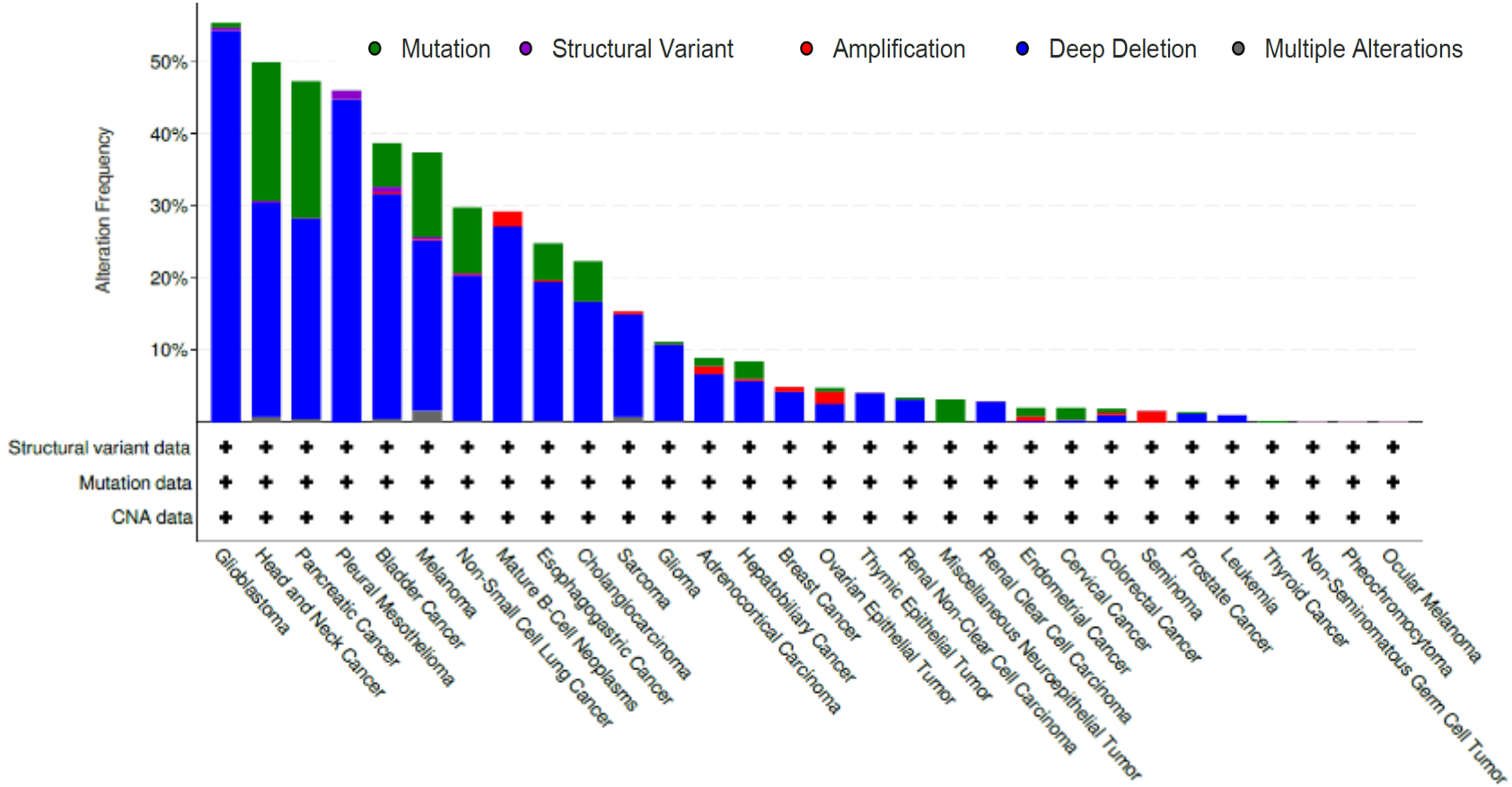
- Dysregulated CDK4/6 drive cancer progression and proliferation in G1, suggesting a role for CDK4/6 inhibition
- Abemaciclib (CDK4/6i) activity in *CDKN2A* mutant cells is limited by CDK2 bypass of CDK4/6 inhibition [1]

CDKN2A also encodes p14^{ARF}, which disrupts MDM2-directed degradation of p53; suppression of MDM2 expression by CDK9i may compensate for loss of this activity

No approved drugs for patients harboring CDKN2A/ CDKN2B

[1] *Gong, Cancer Cell 2017, 32, 761.*

CDKN2A Alterations

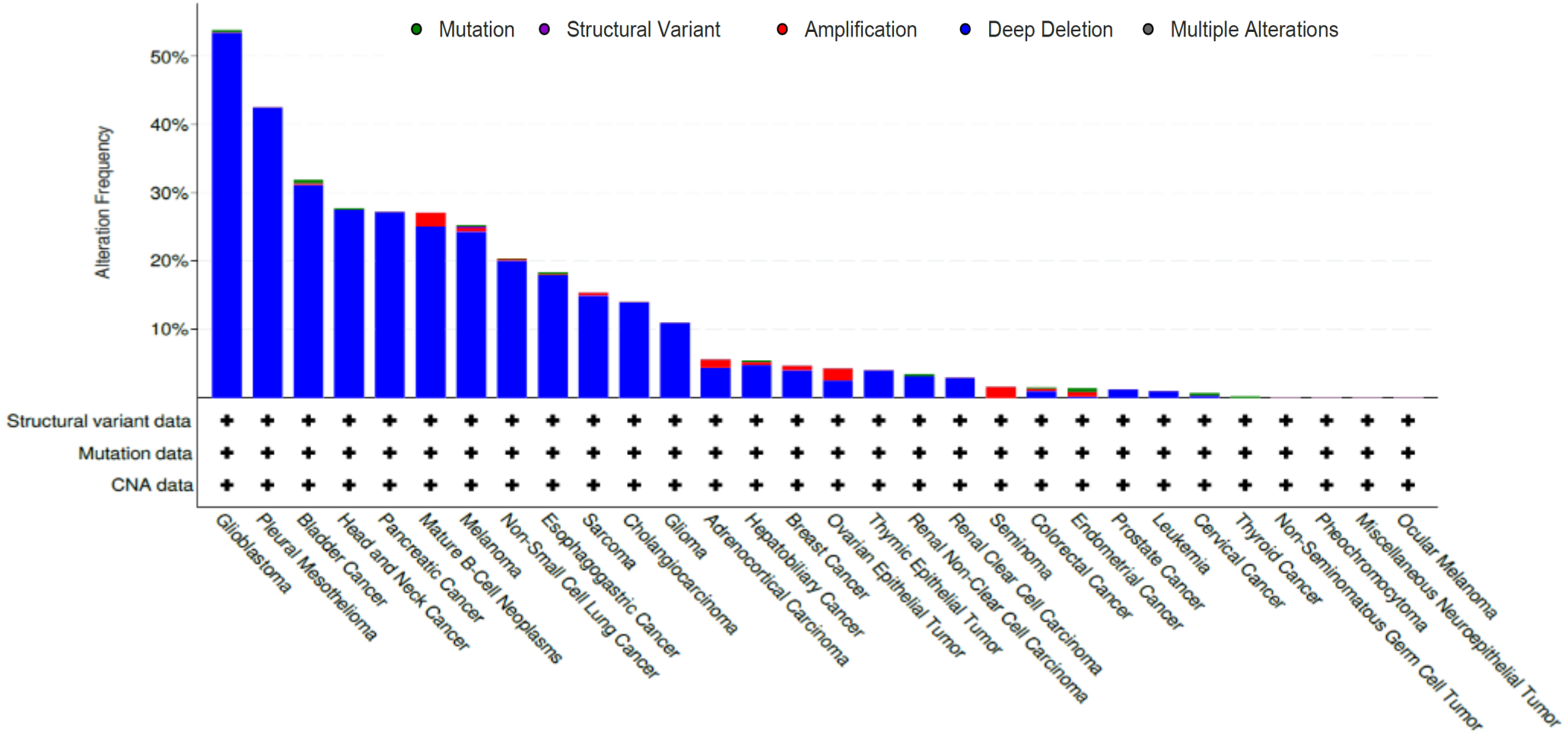


Solid tumors >10%: GBM, H&N, pancreas, esophagus, lung, bladder, HCC/BTC, breast, melanoma, sarcoma

Lymphoma: CDKN2A deletions in 46% of PTCL-NOS patients.

cBioportal, dl 23OCT23. Maura F et al Haematologica. 2021 Nov 1 106 11 2918

CDKN2B Alterations



>10%: glioma, lung, bladder, H&N, pancreas, melanoma, esophagus, sarcoma, HCC/BTC, breast, ovarian

cBioportal, dl 23OCT23.

Fadra Oral 065-101 Ph 1/2 Solid Tumors & Lymphoma *(ongoing, unselected, late line)*

Enrolled n=47 as of March 26, 2024. No DLT in cohorts 1-5 (n=22). DL5=RP2D. PoC part to start next.

Dose Escalation* (3+3; unselected, all comer, late line; DL= dose level)

DL6B (n=10) *150mg qd tabs 7d (4/4 wk)*	✓
DL6A (n=13) *125mg bid tabs M to F (4/4 wk)*	✓
DL6 (n=2) *150mg bid caps M to F (4/4 wk)*	✓
DL5 (n=9) *100mg bid caps M to F (4/4 wk)*	✓
DL4 (n=3) *100mg bid caps M to F (3/4 wk)*	✓
DL3 (n=3) *75mg bid caps M to F (3/4 wk)*	✓
DL2 (n=4) *50mg bid caps M to F (3/4 wk)*	✓
Starting DL (n=3) *50mg bid caps MWF (3/4 wk)*	✓

Proof of Concept (PoC)** (Simon 2-stage; 2nd /3rd line)

Cohort 1: Endometrial, Ovarian

Cohort 2: Biliary / cholangiocarcinoma

Cohort 3: Hepatocellular Carcinoma

Cohort 4: Breast (post-CDK4/6i, TNBC, HER-2 refractory)

Cohorts 5, 6: Lymphoma (T-cell; B-cell)

Cohort 7: mCRC (including KRAS mutated)

Cohort 8 Basket: biomarker selected (related MoA suspected; expand if PR seen)

Pivotal (if randomized study not needed)

Single-arm, open label, study for n=TBD cancer patients in a histology from PoC

Pivotal indication to be determined based on clinical data from PoC

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Single agent. Single agent; followed by combination. ClinicalTrials.gov Identifier: NCT04983810.*

Oral Fadra Safety Summary

- All dose levels
  - Mostly grade 1 and 2 and reversible
    - Gastrointestinal disorders, including nausea, vomiting, diarrhea, and constipation
    - General, including fatigue
    - Metabolism, including hyperglycemia
    - Hematological, including platelet decrease

- Dose limiting toxicities (DLT) observed at 125mg BID and higher
  - Grade 3 nausea and hyperglycemia; both manageable and reversible

- Dose levels 1-5 were well tolerated with no DLTs reported

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Data on file.

Oral Fadra 065-101 Response *(all comer, n=32, as of 31JAN24)*

AMT = Appendix

CC = Cervix

CRC = Colon & Rectum

CTCL = Cutaneous T Cell Lymphoma

EC = Uterus

ICC = Intrahepatic bile ducts

GBC& EHBDC = Gallbladder and Extrahepatic bile ducts

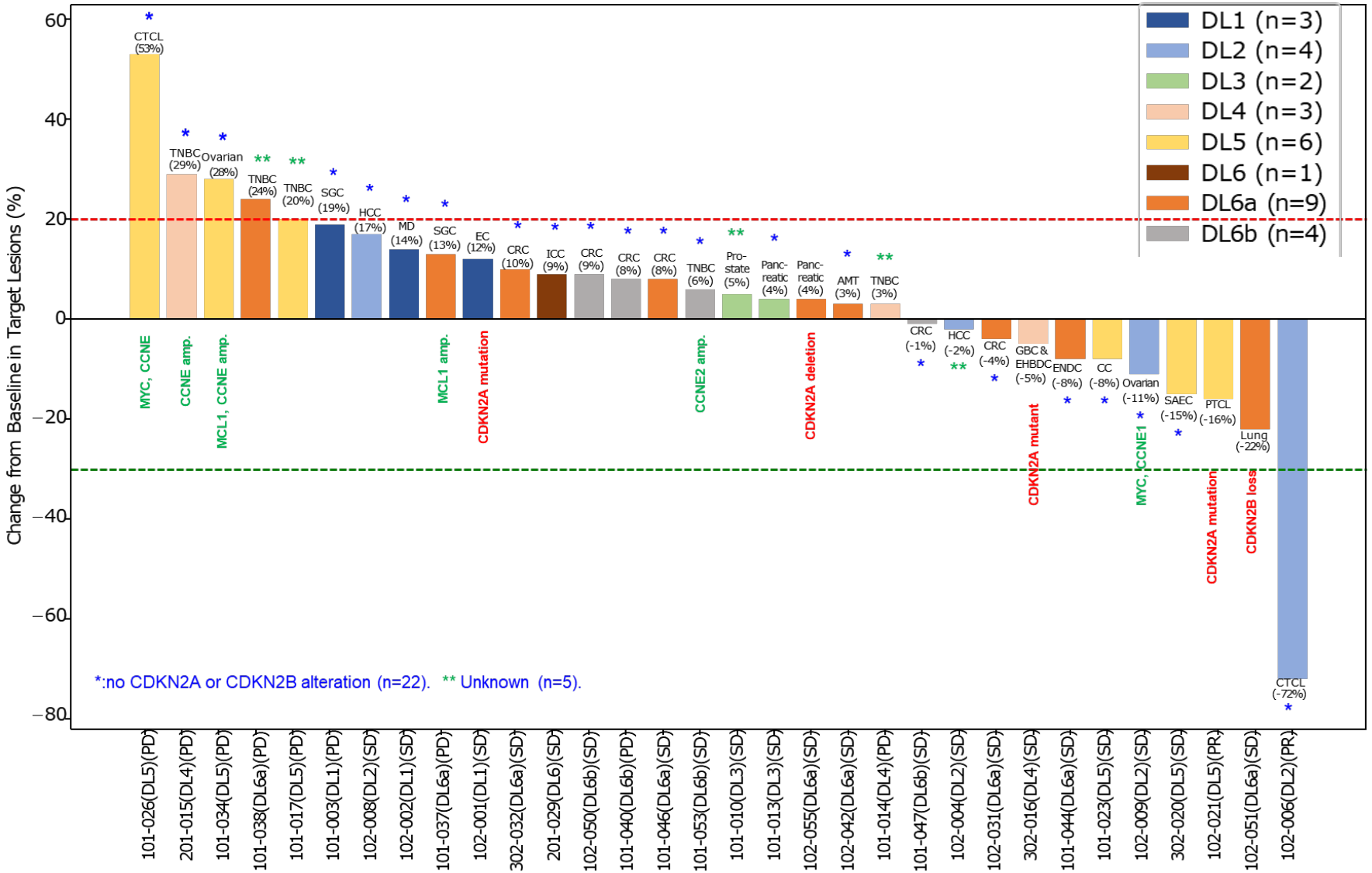
ENDC = Endometrioid
MD = Mandible

SAEC = Serous Adenocarcinoma of the Endometrium

SGC = Salivary glands

HCC = Liver

TNBC = Triple-Negative Breast Cancer



Evaluable for response by:

- **RECIST 1.1 (n=29)**
- **mSWAT (n=1)**
- **Lugano (n=2)**

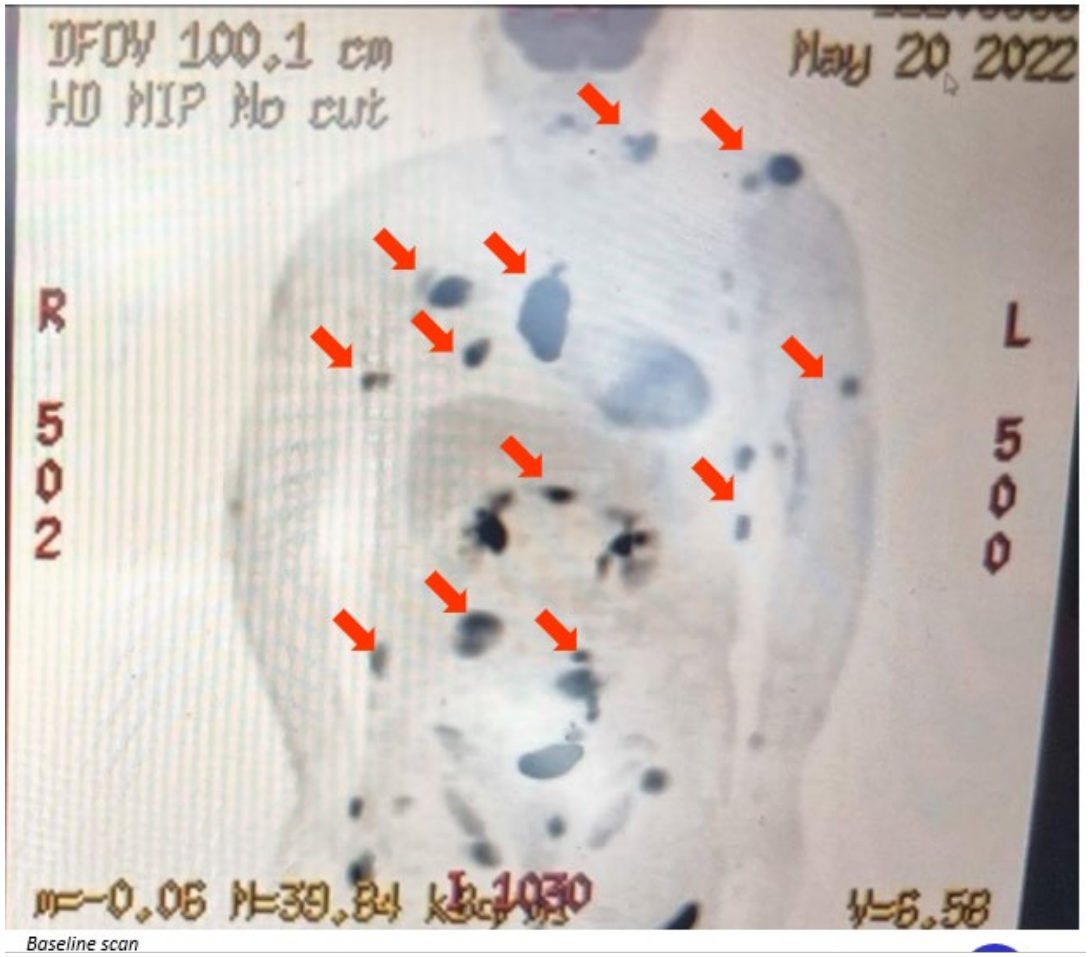
PR (n=2)

SD (n=21)

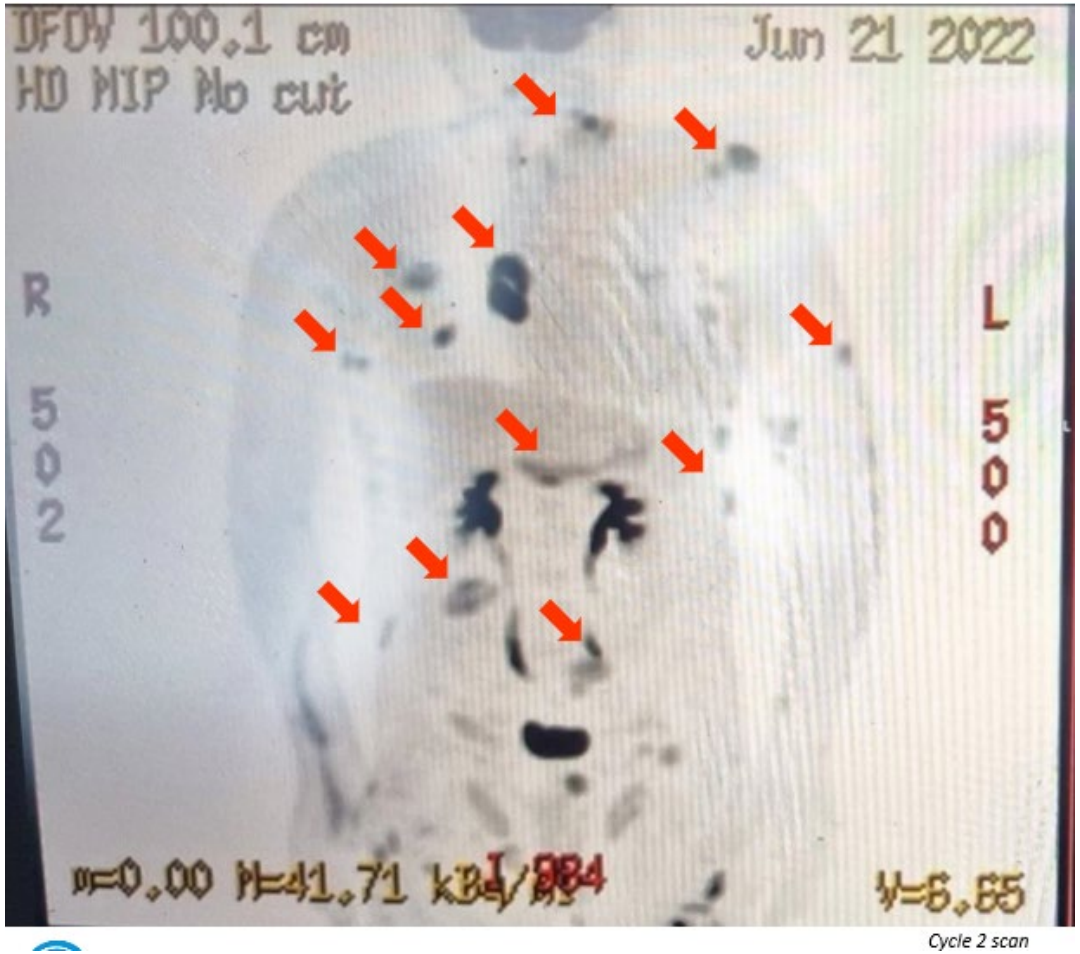
PD (n=9)

*Best % change from baseline in target lesions. 101-012 (DL3) no measurable target lesions.*Tumor assessments at 4 weeks post-treatment and every 8 weeks thereafter.*

PR in angioimmunoblastic PTCL pt. *(oral 065-101, 1st cycle DL5, CDKN2A loss)*



Baseline scan



Cycle 2 scan

Data on file. PET scan images kindly provided by the principal investigator. ***CDKN2A deletions in 46% of PTCL-NOS patients,*** *Maura F et al Haematologica. 2021 Nov 1 106 11 2918.*

CDKN2A deletion in T Cell Lymphoma

Incidence of CDKN2A deletions was 46%.[1]

ARTICLE

Non-Hodgkin Lymphoma

Ferrata Storti Foundation

Haematologica 2021
Volume 106(11):2918-2926

CDKN2A deletion is a frequent event associated with poor outcome in patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)

Francesco Maura,[1-4] Anna Dodero,[5] Cristiana Carniti,[5] Niccolò Bolli,[2,5] Martina Magni,[5] Valentina Monti,[6] Antonello Cabras,[6] Daniel Leongamornlert,[3] Federico Abascal,[3] Benjamin Diamond,[1] Bernardo Rodriguez-Martin,[7] Jorge Zamora,[7] Adam Butler,[3] Inigo Martincorena,[3] Jose M. C. Tubio,[7] Peter J. Campbell,[3] Annalisa Chiappella,[8*] Giancarlo Pruneri[2,6] and Paolo Corradini[2,5]

[1]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [3]The Cancer, Aging and Somatic Mutation Program, Wellcome Sanger Institute, Hinxton, Cambridgeshire, UK; [4]Weill Cornell Medical College, New York, NY, USA; [5]Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [7]CIMUS - Molecular Medicine and Chronic Diseases Research Center, University of Santiago de Compostela, Santiago de Compostela, Spain and [8]Department of Hematology Azienda Ospedaliera Città della Salute e della Scienza, Turin, Italy.

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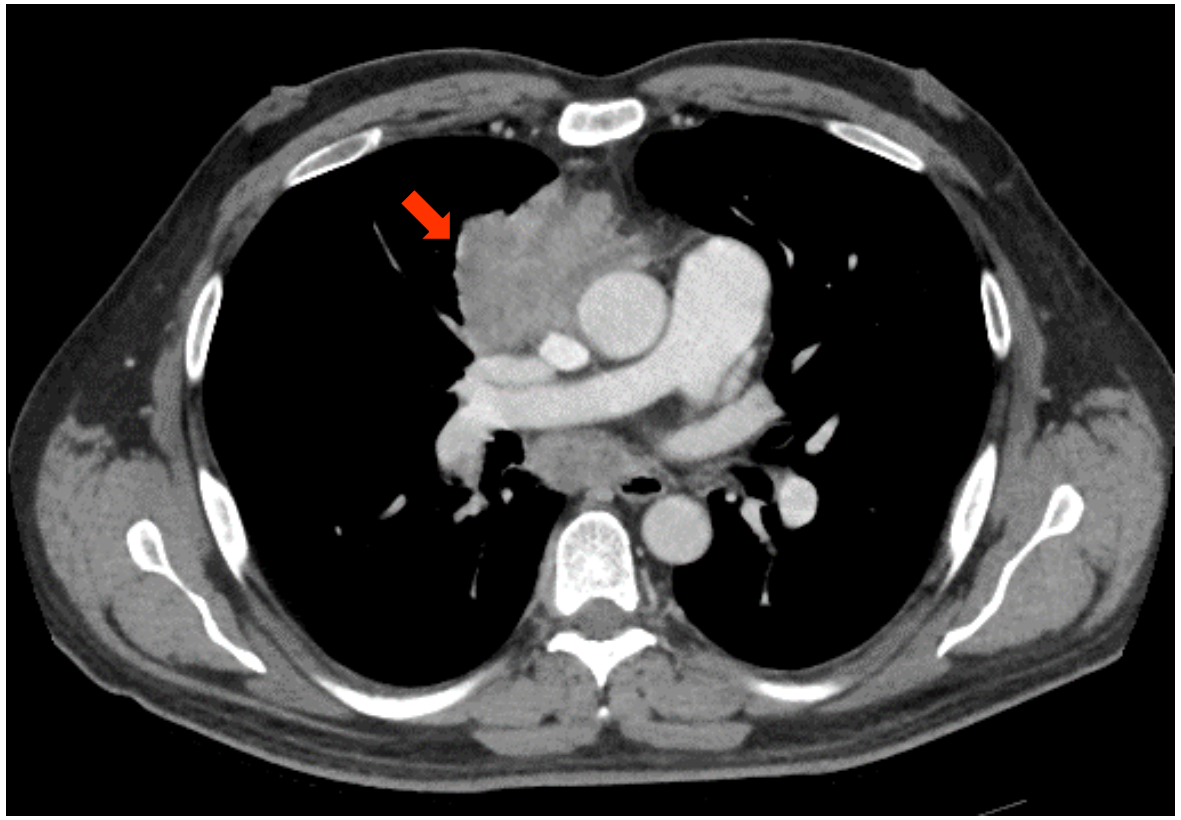
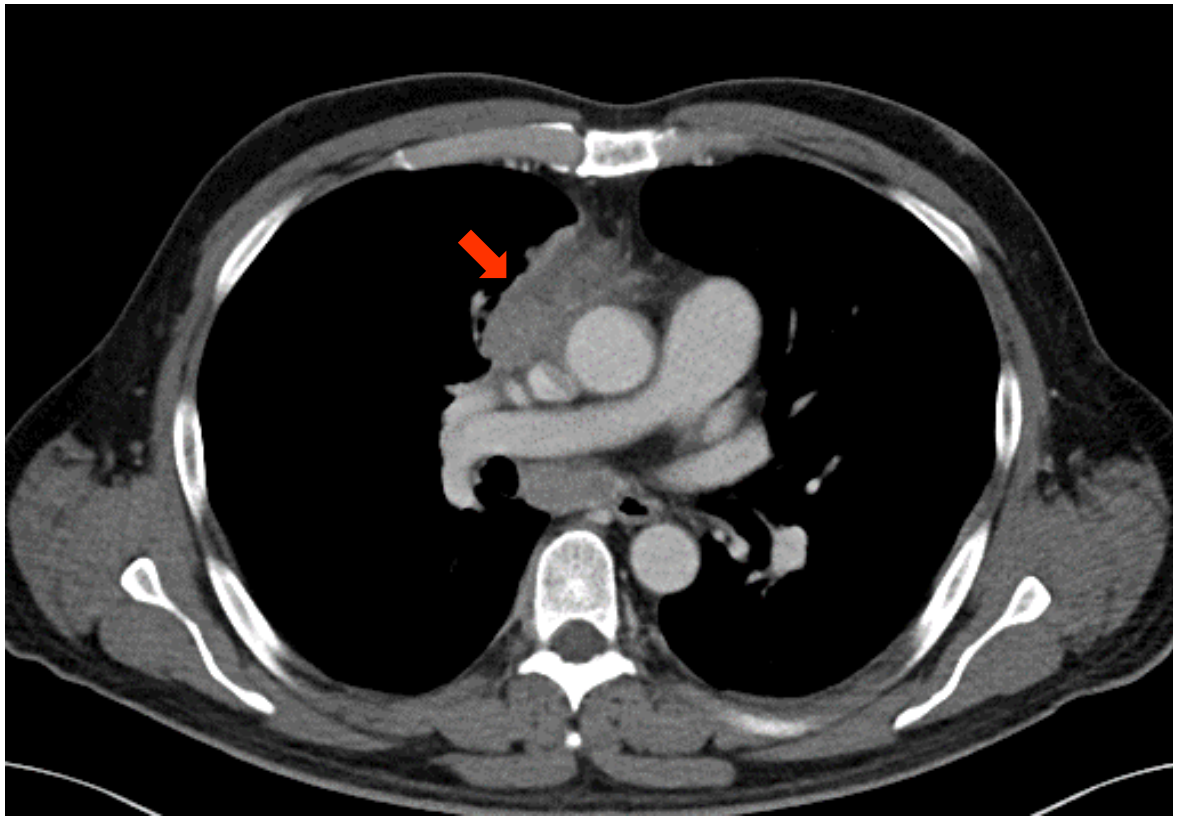
[1] *Maura F et al Haematologica. 2021 Nov 1 106 11 2918.*

Squamous NSCLC patient *(oral 065-101, 1 cycle DL6a)*



Baseline scan 7-SEP-23

50y old, NOV22-APR23 carboplatin+paclitaxel; MAY23 atezolizumab+docetaxel, progressed



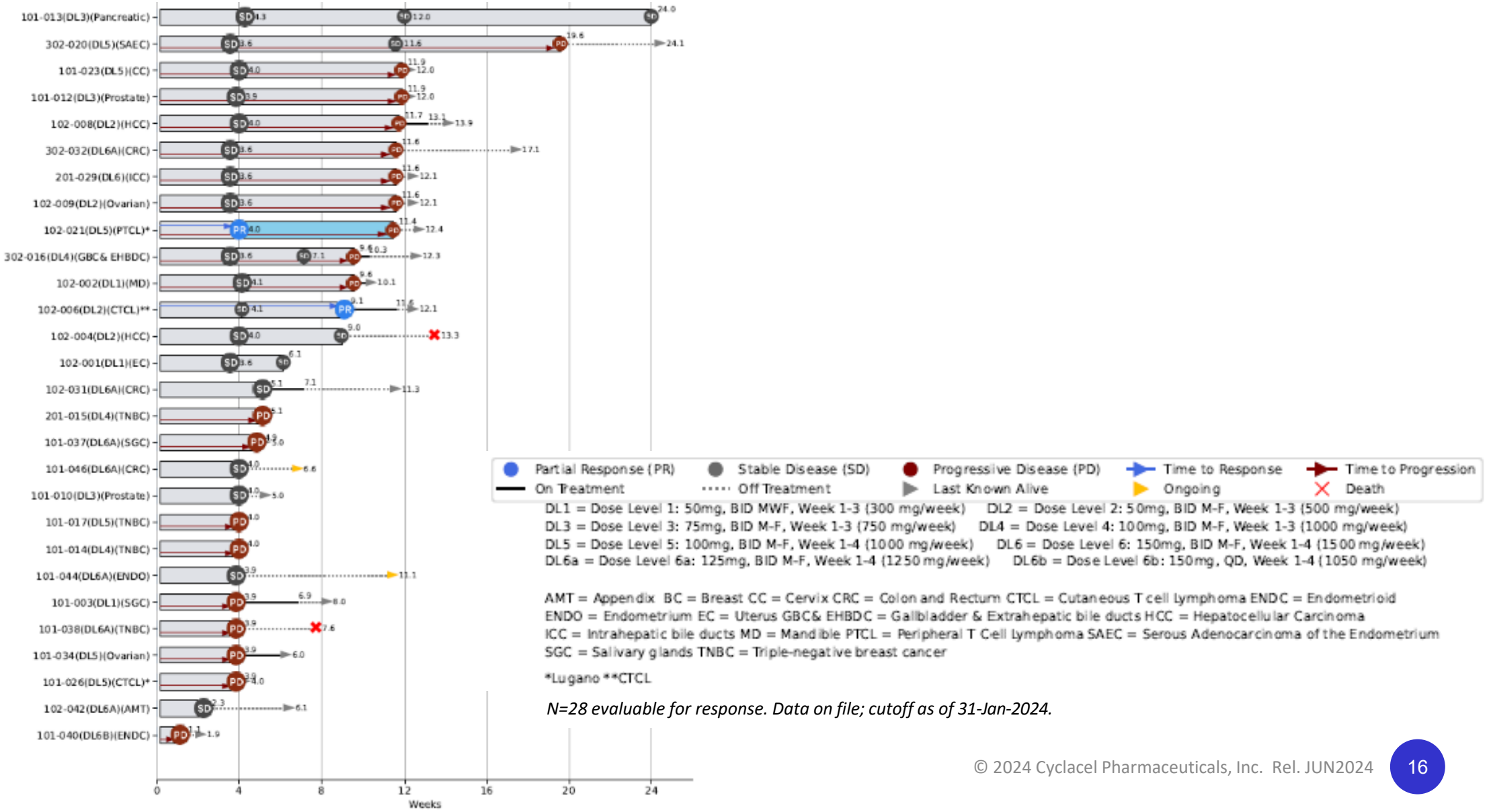
Cycle 1 scan 9-OCT-23

*SD sum of all target lesions **-22**%. D1C1 14-SEP-23*

NGS: CDKN2B loss

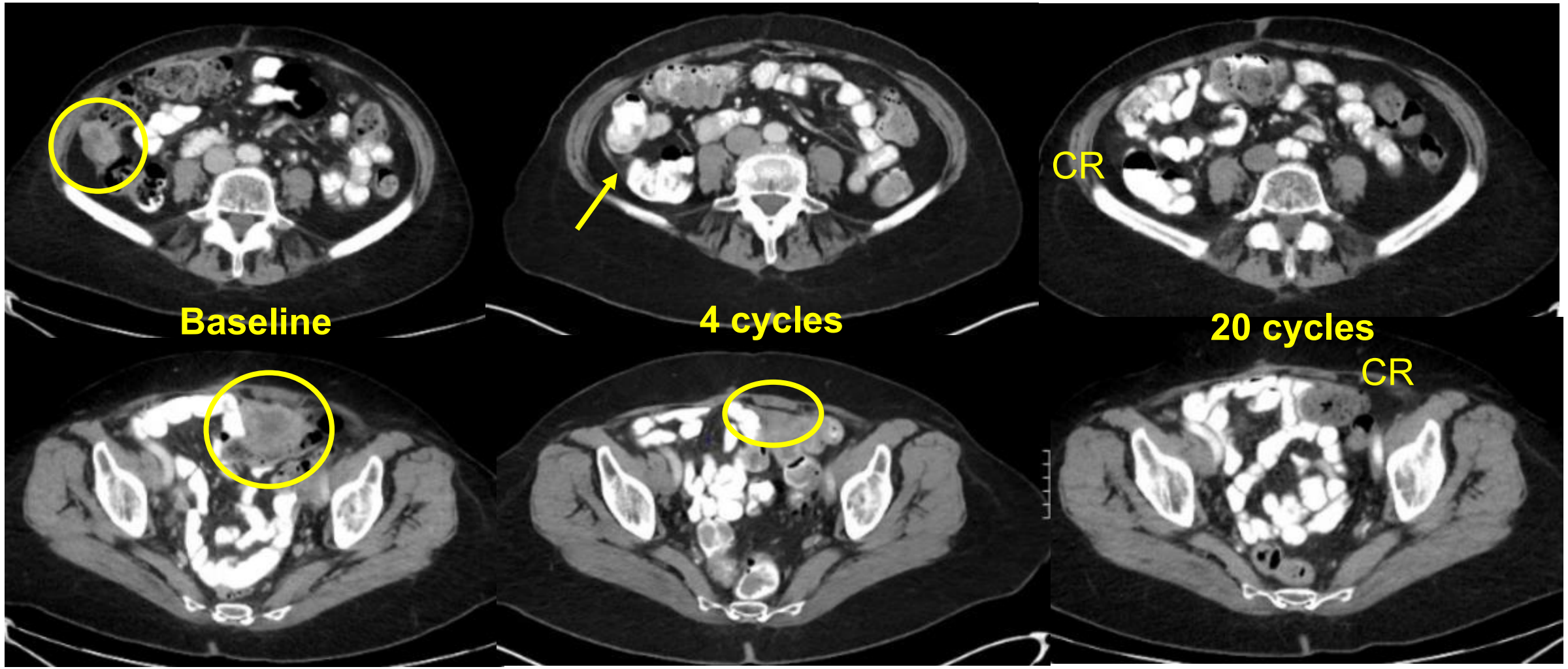
CYCLACEL® *Data on file. CT scan images kindly provided by the principal investigator.*

Fadra Oral 065-101 Swimmers Plot *(dose escalation part)*



N=28 evaluable for response. Data on file; cutoff as of 31-Jan-2024.

PR then CR 065-01 Part 2 IV Endometrial Pt *(CDKN2A, CDKN2B and MTAP loss)*



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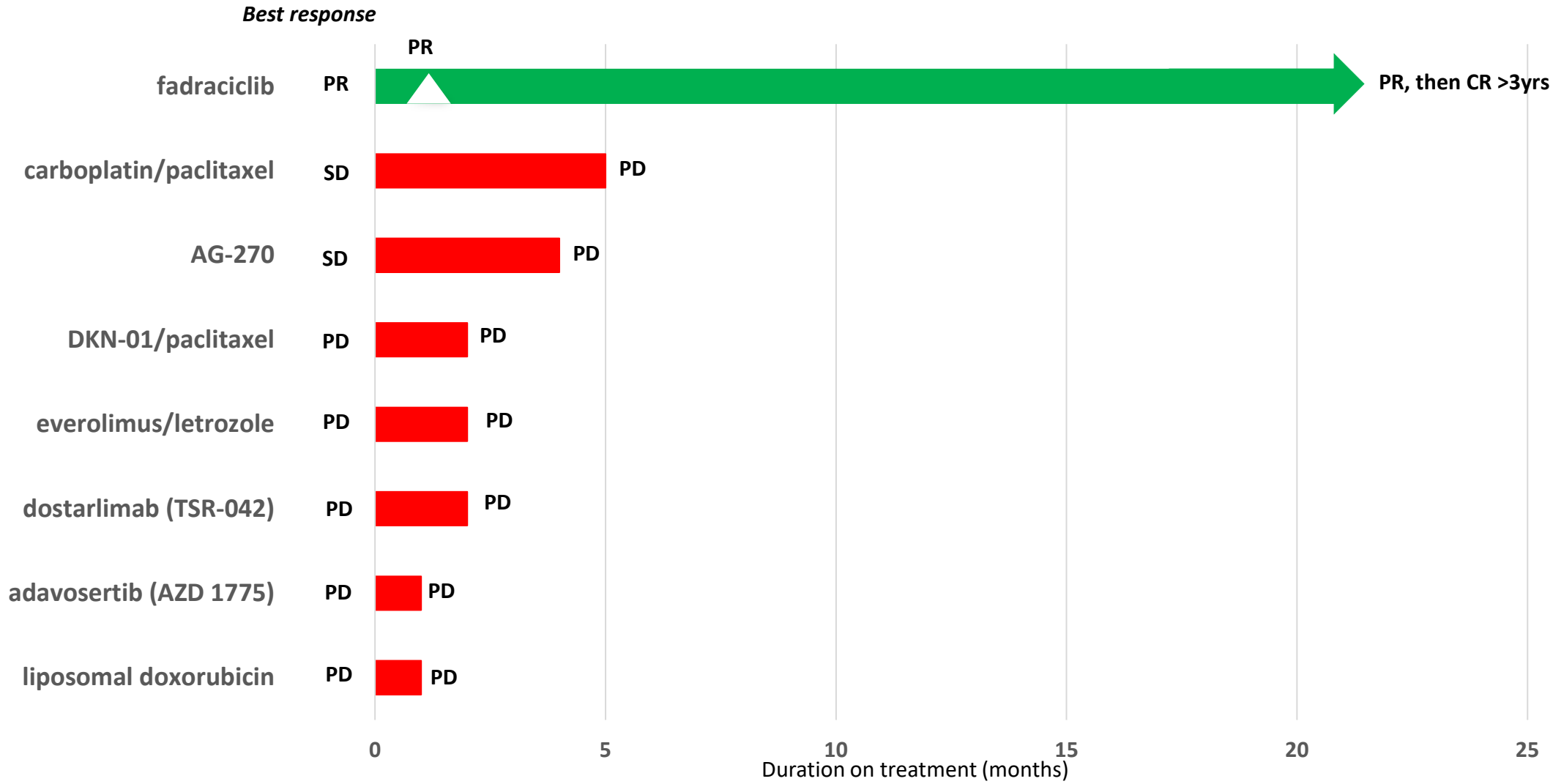
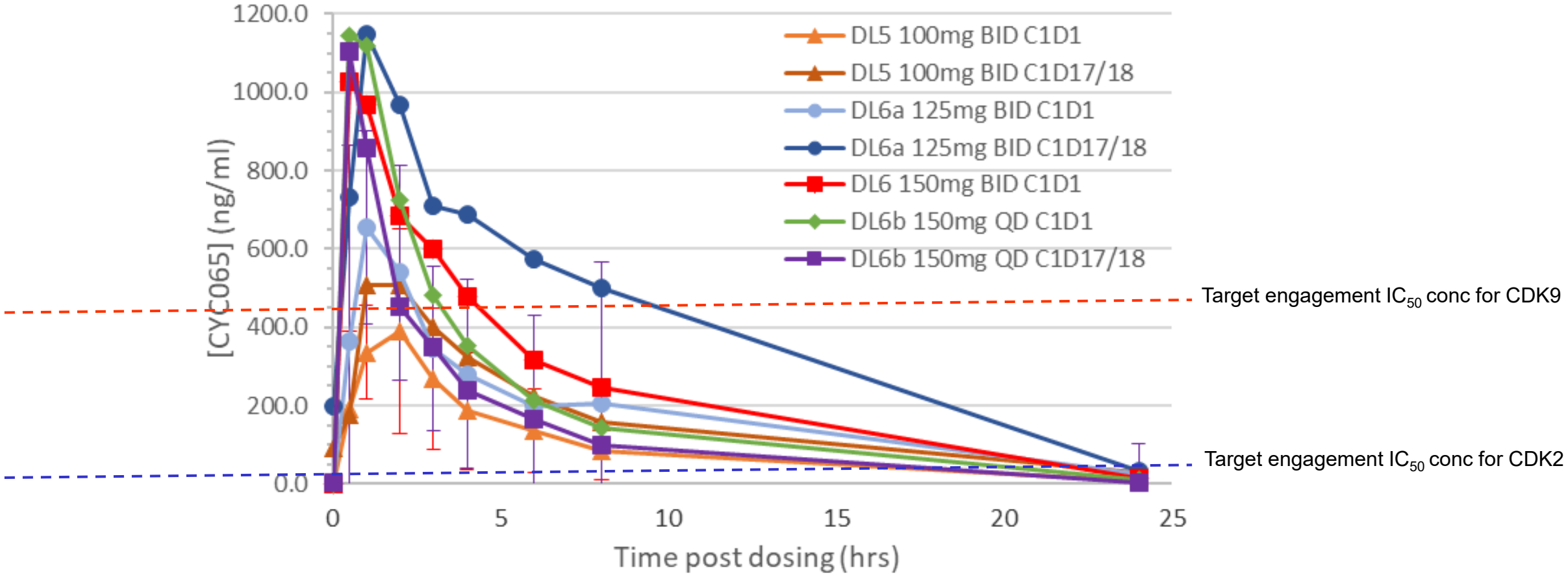
Do, KT, et al., 32nd EORTC/AACR/NCI Virtual Symposium 24-25 Oct. 2020. CR=complete response.

Endometrial Patient History 065-01 Part 2 IV



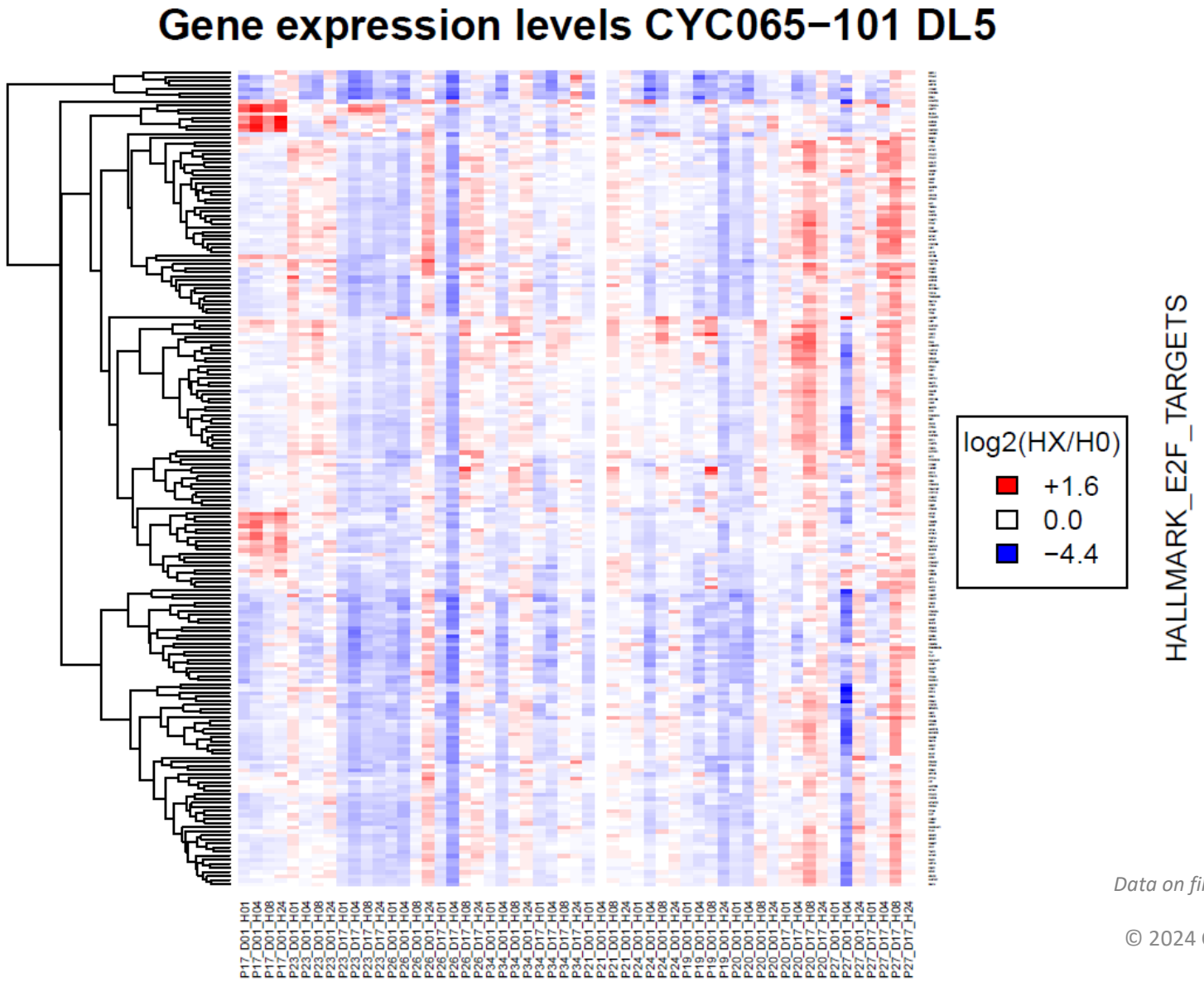
Data on file. Do, KT, et al., 32nd EORTC/AACR/NCI Virtual Symposium 24-25 Oct. 2020. PD=progressive disease. SD=stable disease.

Dose Proportional PK with CDK2 and 9 Coverage at Higher Dose Levels



Data on file. NB Single dose given on D1 and D17/18.

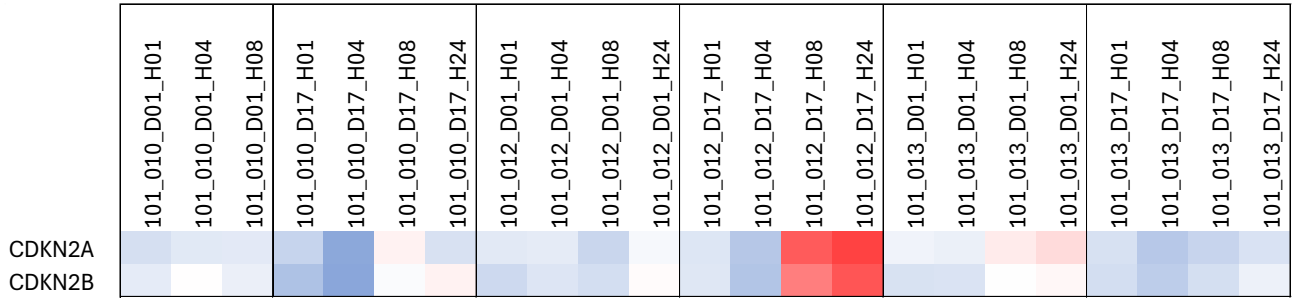
Fadra Suppresses E2F (CDK2 dependent) DL5 Phase 1 Patients



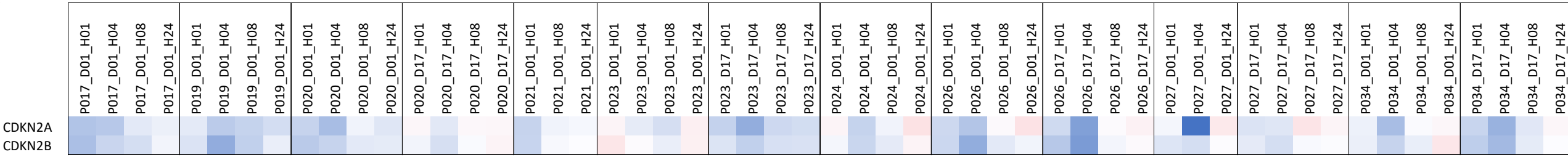
Data on file. Blue=suppression, Red=overexpression.

Fadra Suppresses CDKN2A/B Transcription in Patients

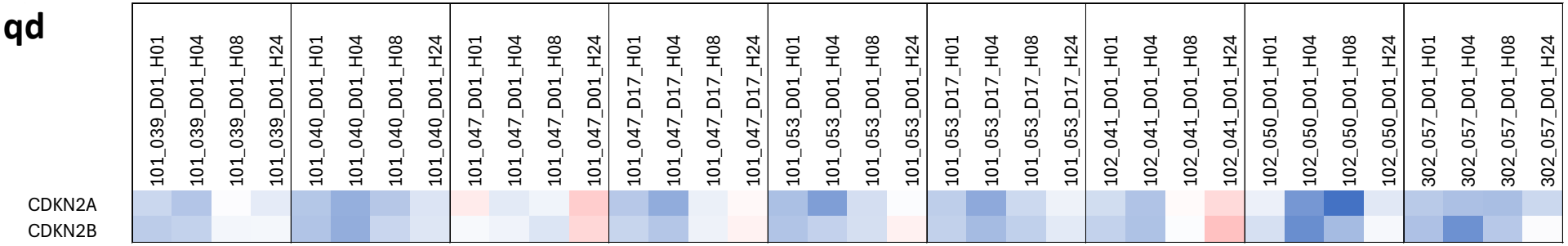
DL2: 50 mg bid

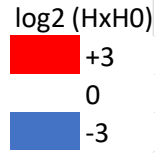


DL5: 100 mg bid



DL6b: 150 mg qd





Data on file. RNAseq transcript data.

Potential for Oral Fadra as Precision Medicine

Single agent responses and broad activity in liquid and solid cancers

CDK2 + CDK9 inhibition may be superior to either CDK2 or CDK9

- Cancer cells adapt to CDK2i; CDK2i work better if CDK9i silences MYC
- Exploiting CDKN2A/B vulnerability for precision medicine strategy
- **Fadra** unusual next gen CDKi; has threaded the needle of transient suppression of anti-apoptosis proteins without broad hematological toxicity

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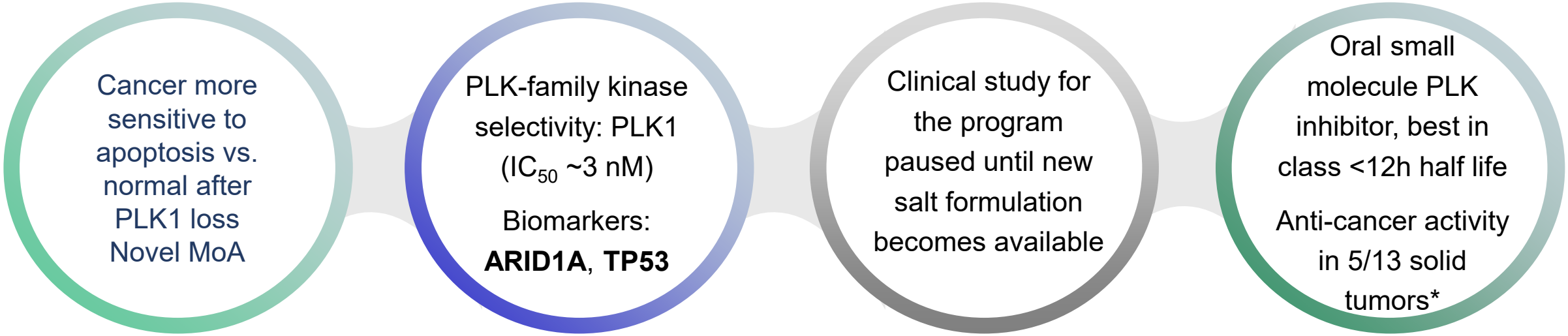
Arora M et al, Cancer Res 2023 83 (7_Suppl): 5992. Knudsen E et al Cell Rep 2022 Mar 1 38 9. Poon E et al, JCI 2020.

Plogosertib (CYC140) Next Gen PLK1 inhibitor

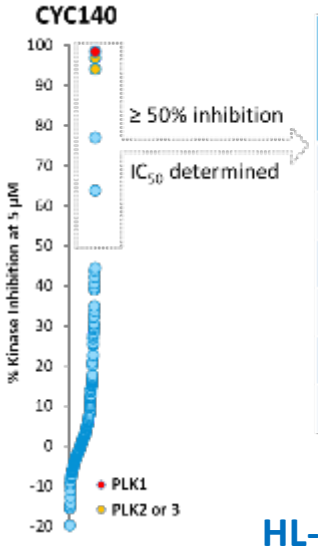


Novel mechanism with a unique **mutational** strategy

Targeting ARID1A and TP53 Mutated Cancers

Plogo Preclinical Activity

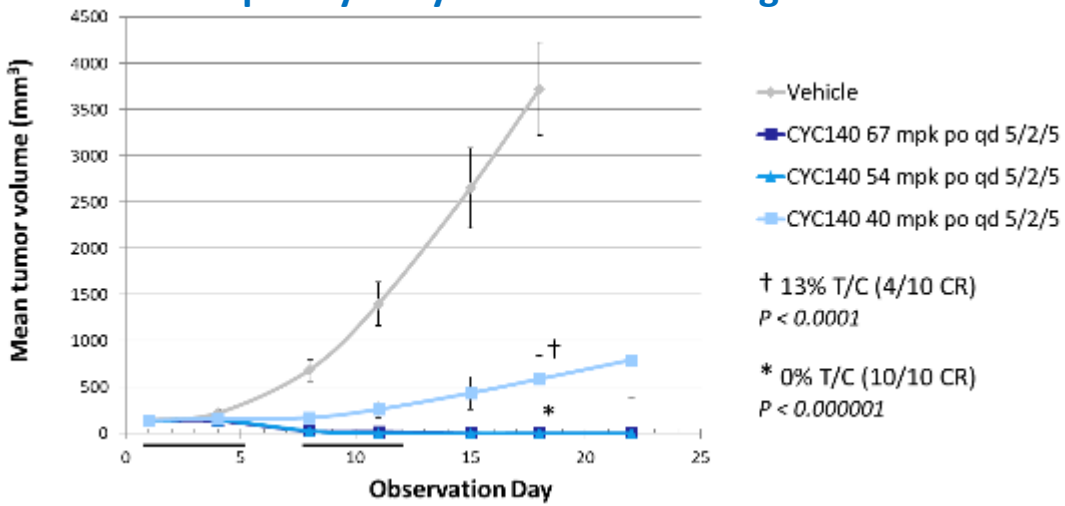
Kinase Profile



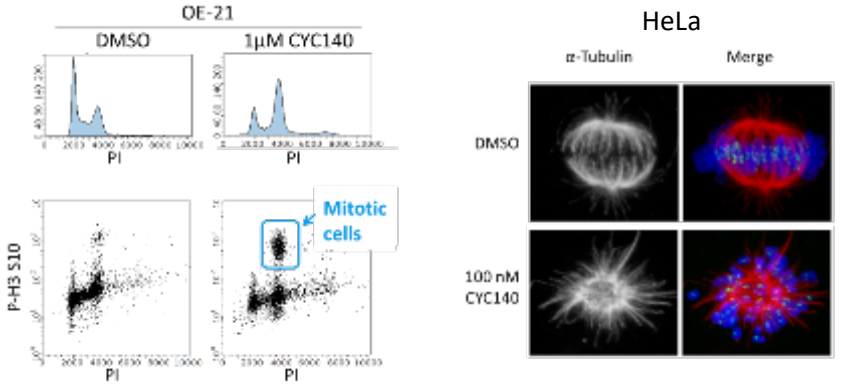
Kinase	CYC140 IC_{50} (nM)	PLK1 Selectivity (fold)
PLK1	2.7	1
PLK2	155	58
EIF2AK3	292	109
PLK3	297	112
CaMK2δ	1630	612
DAPK1	2860	1074

PLK1 inhibition

HL-60 promyelocytic leukemia xenograft



CYC140 increases mitotic cell number and induces monopolar spindle formation



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Moureau, ENA 2016 Abs355; Moureau, AACR 2017 Abs 4178.

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 likely due to myelosuppression; long terminal half-life ~110h
- Dose intensity led to single agent activity
- Epigenetic activity incl. BRD4 inhibition

Onvansertib

(Cardiff; p.o., selectivity primarily PLK1, secondarily CDK9, etc.*)

- Signal in KRASmut mCRC with bevacizumab/FOLFIRI; terminal $t_{1/2}$ ~24h
- Ph 1b: *AML w/chemo; prostate w/ abiraterone*; mPDAC w/chemo; SCLC
- Ph 2: mCRC 3 arm RCT 2 doses triplet therapy vs control bevacizumab/chemo (n=90)

Plogosertib

(Cyclacel; p.o., selectivity primarily PLK1, secondarily PLK2, PLK3)

- Preclinical activity in multiple solid tumors and leukemias; terminal $t_{1/2}$ ~11h
- Single agent anticancer activity in NSCLC, ovarian, biliary, ACC, etc. (4 dose levels)
- Epigenetic MoA incl. BRD4 inhibition: modulating novel cancer pathways

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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.*

Plogo 140-101 Oral Ph1/2 Ongoing in Solid Tumors & Lymphoma

Dose Escalation* (3+3; all comer, late line; DL=dose level)

	Active
DL7 (n=3) *20mg qd M to F (wk 1 to 3)*	
DL6 (n=3) *20mg qd M to F (wk 1 & 3)*	
DL5 (n=3) *15mg qd M to F (wk 1 to 3)*	
DL4 (n=3) *15mg qd M to F (wk 1 & 3)*	✓
DL3 (n=3) *10mg qd M to F (wk 1 to 3)*	✓
DL2 (n=3) *10mg qd M to F (wk 1 & 3)*	✓
Starting DL (n=3) *5mg qd M to F (wk 1 to 3)*	✓

Schedule: 3 out of 4 wk per cycle.

Proof of Concept (PoC)**

(Simon 2-stage; 2nd /3rd line)

Cohort 1: Bladder cancer

Cohort 2: Breast cancer (TNBC)

Cohort 3: Lung cancer (NSCLC and SCLC)

Cohort 4: Hepatocellular carcinoma (HCC) and biliary tract cancer

Cohort 5: Metastatic colorectal cancer (mCRC) including KRAS-mutated

Cohort 6: B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL)

Cohort 7: T-cell lymphoma (CTCL/PTCL)

Cohort 8 Basket: tumors suspected to have related MoA (expand if responses)

Pivotal

(if randomized study not needed)

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. ClinicalTrials.gov Identifier: NCT053583790*

Oral Plogo Well Tolerated up to Dose Level 5

- Drug-related adverse events reported, mostly grade 1 and 2 and reversible
  - General including fatigue
  - Hematological: anemia
  - Investigations: mild transaminase increase

- No dose limiting toxicities observed to date

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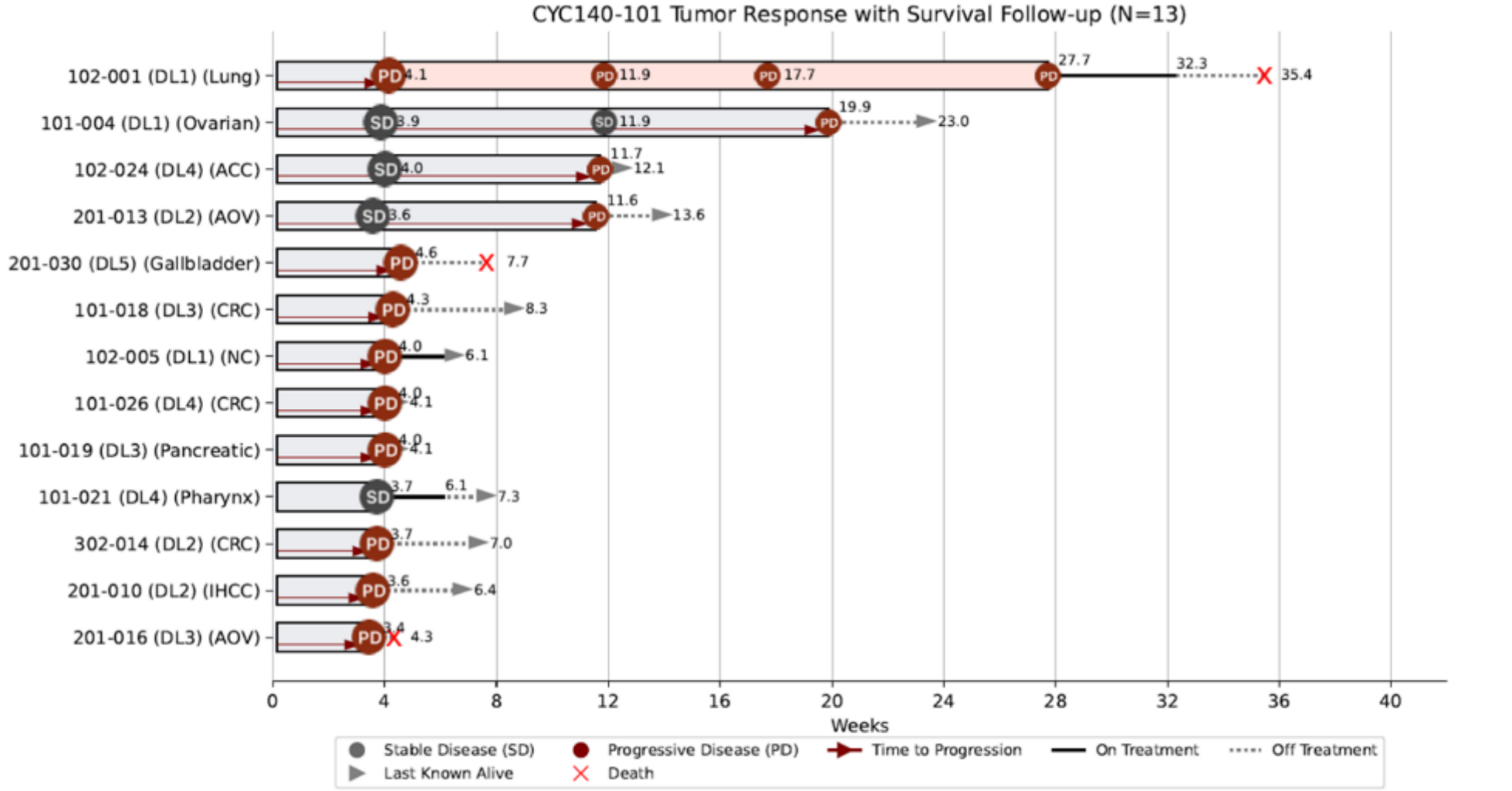
Data on file.

Plogo Oral 140-101 DL1-4 Swimmers Plot *(dose escalation ongoing)*



DL1 = Dose Level 1: 50mg, BID MWF, Week 1-3 (300 mg/week) DL2 = Dose Level 2: 50mg, BID M-F, Week 1-3 (500 mg/week) DL3 = Dose Level 3: 75mg, BID M-F, Week 1-3 (750 mg/week)
DL4 = Dose Level 4: 100mg, BID M-F, Week 1-3 (1000 mg/week) DL5 = Dose Level 5: 100mg, BID M-F, Week 1-4 (1000 mg/week)
ACC = Adenoid Cystic Carcinoma (Salivary glands) AOV = Ampulla of Vater CRC = Colon and Rectum IHCC = Intrahepatic cholangiocarcinoma NC = NUT carcinoma (Paranasal sinuses)
Data cutoff date: 2023-10-02

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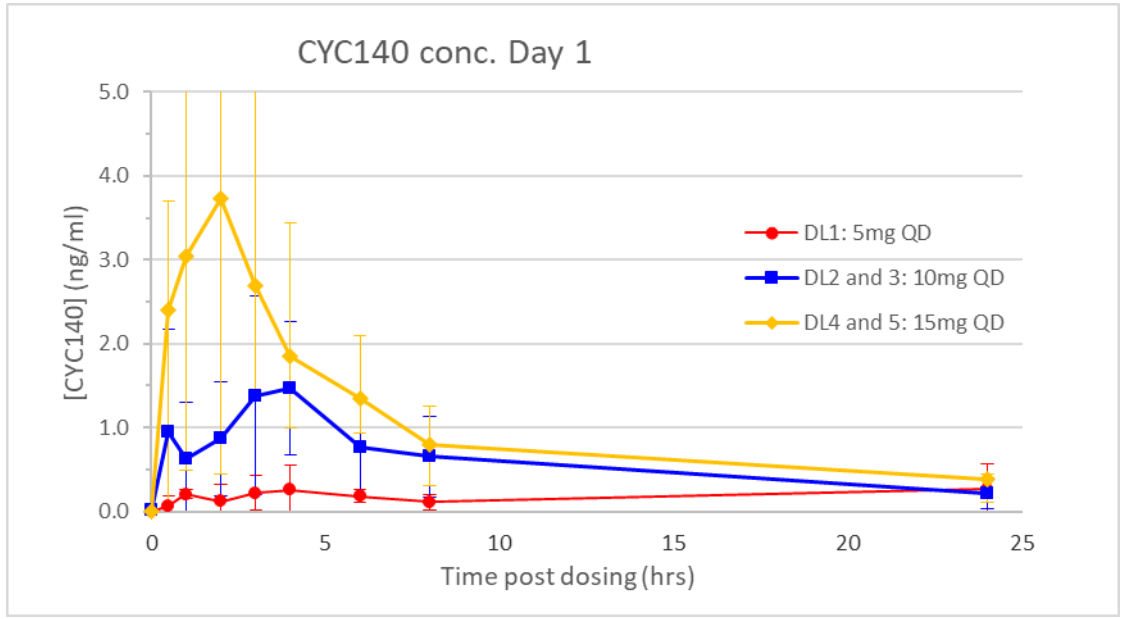
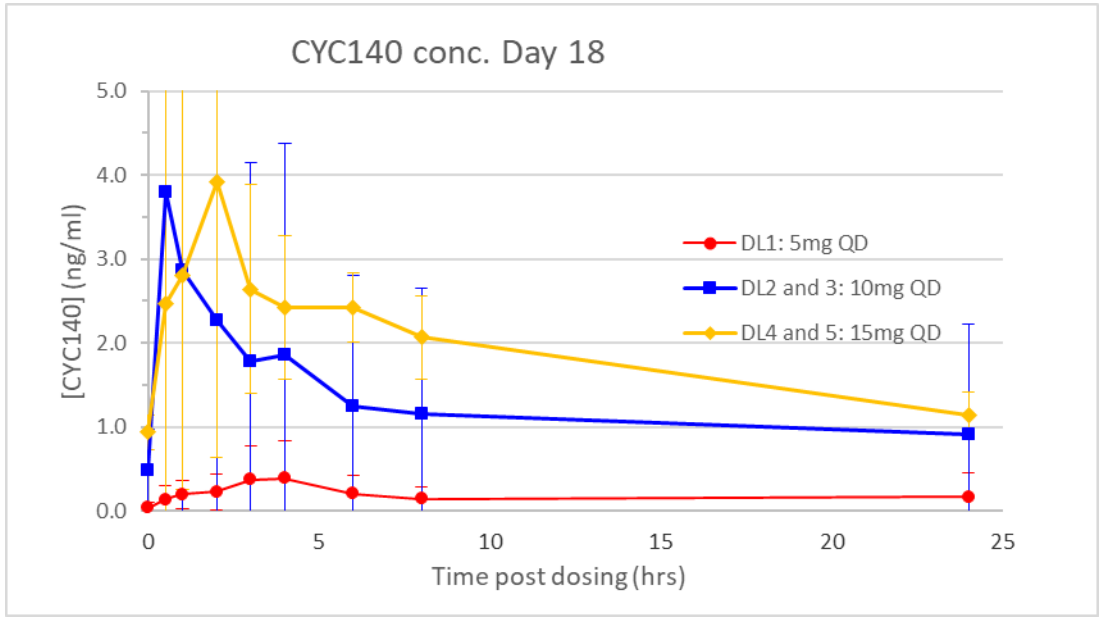
Data on file.

Mean (±SD) Plasma Plogo Concentration-Time Plot C1D1 & C1D18

Day 1



Day 18



Based on preclinical modeling data, efficacious doses yet to be achieved.

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Data on file.

Plogo Conventional Dose Escalation Strategy

Potential activity across mechanistically relevant tumors

- Specific mutations in SWI/SNF complex subunit proteins, incl. ARID1A, SMARCA, etc.
- Novel targets in molecular pathways with unmet medical need
- Could lead to patient selected, biomarker driven Ph1 expansion group

Preclinical sensitivity data from world-class laboratories in CRC, lymphoma, melanoma, ovarian, SCLC.

Requires updated formulation to reach exposure levels

Increased patent exclusivity to 2040

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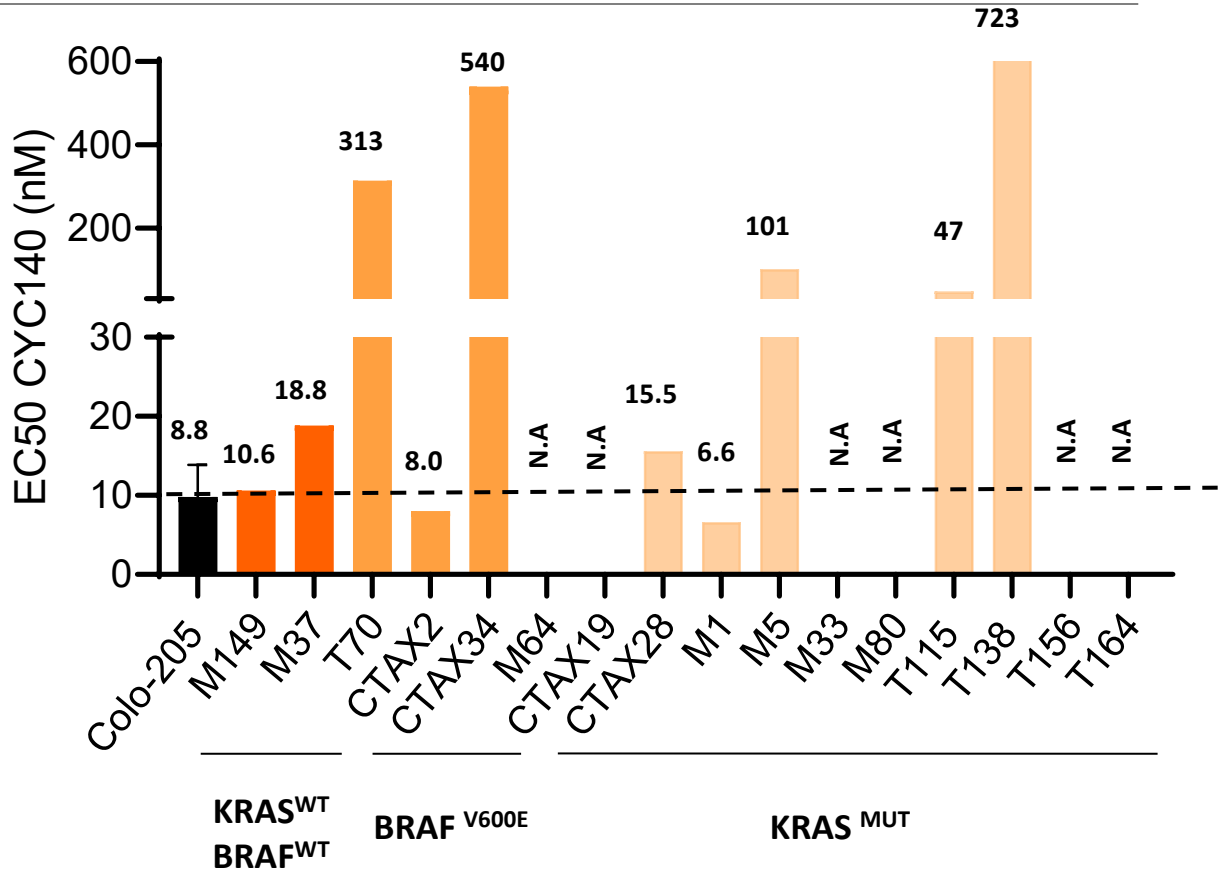
Colorectal PDX Organoid Sensitivity to Plogo

In vitro 3D models from 16 CRC PDX

- 10 $KRAS^{mut}$, 3 $BRAF^{V600E}$, 3 $KRAS^{WT}/BRAF^{WT}$
- Completed EC_{50} by cell viability (19-point dose curve: 0.038 nM – 10 µM)

Sensitivity to plogo:

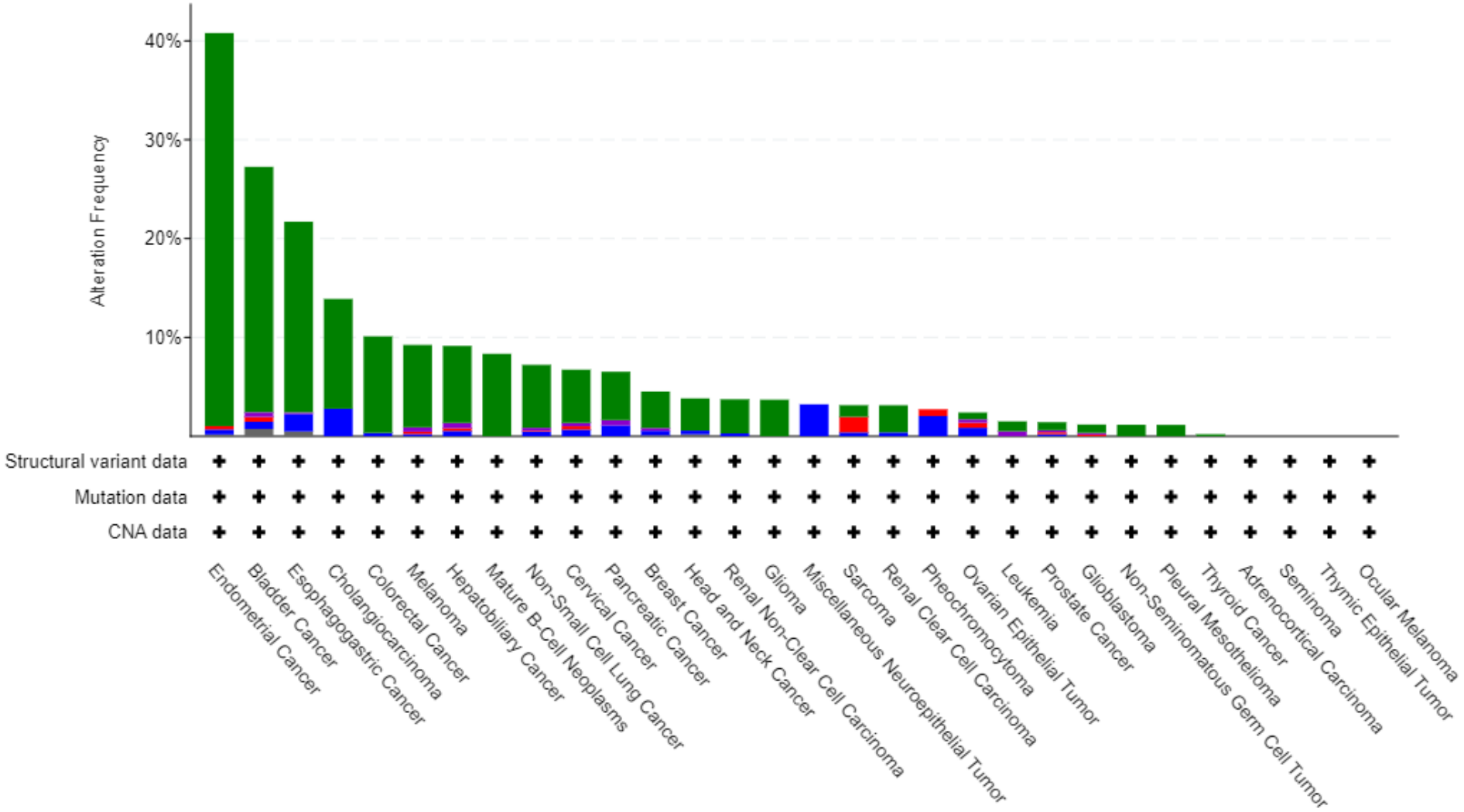
- 5 models with EC_{50} < 30 nM
- Does not appear BRAF or KRAS dependent
- None of resistant are ARID1A mut
- **3/5 sensitives are ARID1A mutant**
- **5/5 sensitives are TP53 mutant**



PDXO	CTAX 19	CTAX 28	M1	M5	M33	M80	T115	T138	T156	T164
KRAS	G12D	G12D	G12D	G13D	G12D	G12C	G12V	G12V	G12C	G12V

Data on file.

ARID1A Modifications



Solid tumors >15%: endometrial, bladder, esophagus, bile duct, colorectal

cBioportal, dl 23OCT23.

Plogo Low Dose Strategy

Epigenetic hypothesis

Plogo enables **chromatin accessibility** at low concentrations

Combination strategy with other epigenetic modulators

- Hypomethylating agents or HDAC Inhibitors

Can use current formulation

Front line opportunity in TP53 mutated AML

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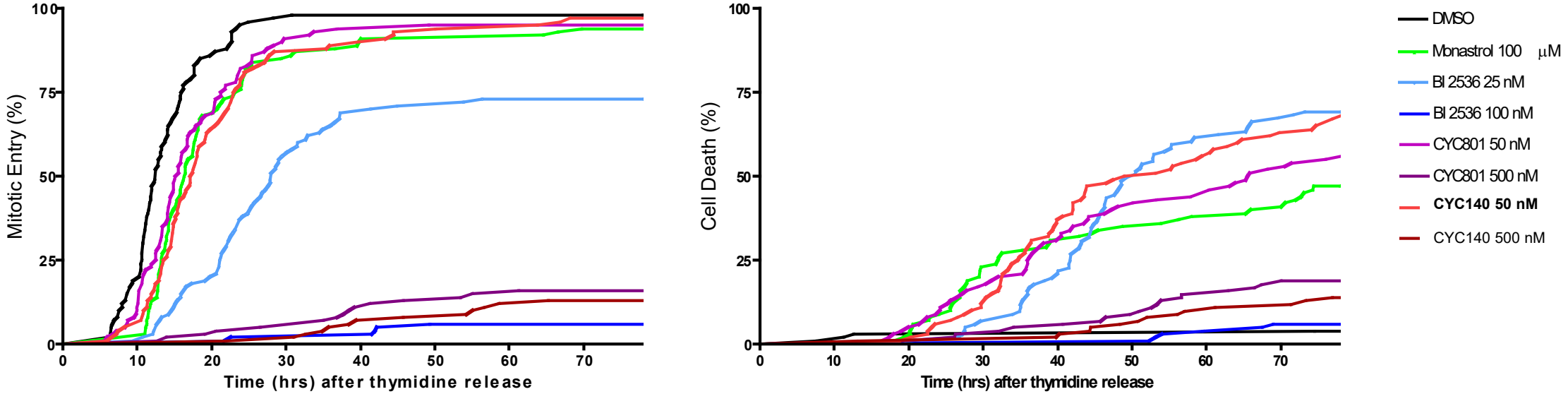
Optimizing PLK1i Exposure May Enhance Cell Death Induction – Rationale for Lower, Prolonged Dosing

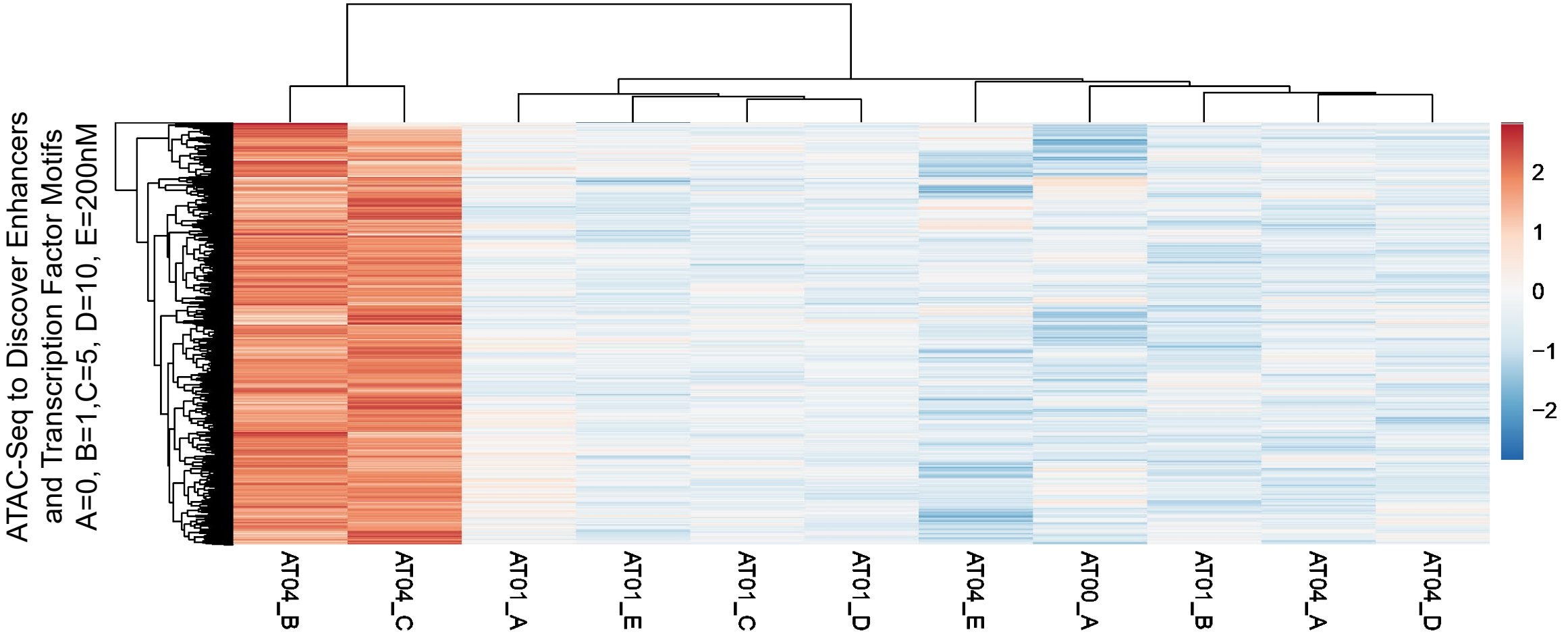
RKO colon carcinoma cell line - Single thymidine block and release prior to treatment



At high doses, PLK1i treatment stops growth; at lower doses PLK1i starts cell cycle and then more tumor cells die.

Aspinal et al., Oncotarget, 2015, 6, 36472-88 and company data on file.

Low Dose Plogo has Dramatic Effect on Chromatin Access



Red: open & transcribing segments. Blue: closed chromatin segments

Data on file. Top 1000 Highly Variable Peaks identified in ATAC seq analysis excluding 24 hrs timepoint.

TP53 Mutated AML Unmet Need

TP53 mutated patients do not benefit from 1L AML Standard of Care:

- venetoclax + azacitidine; poor OS

Ethical to test as 1L treatment in a single arm study

Large unmet medical need

Excellent opportunity for disease modifying treatment

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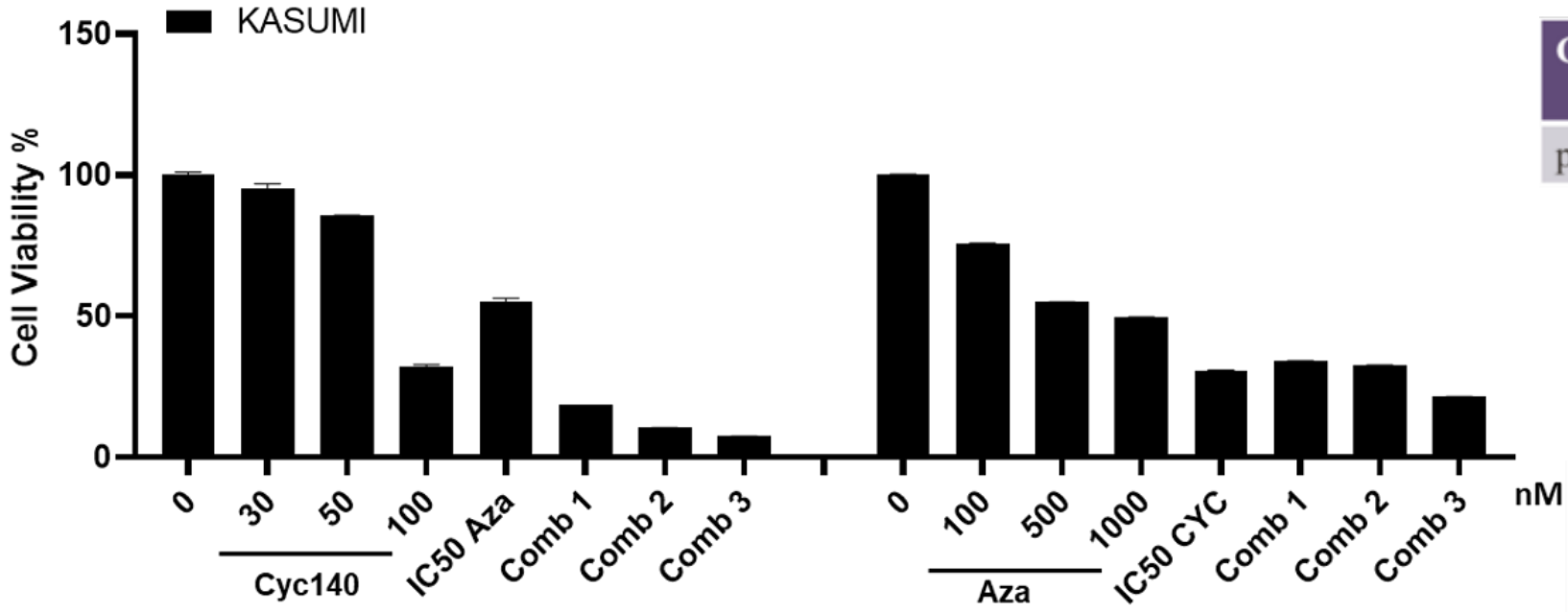
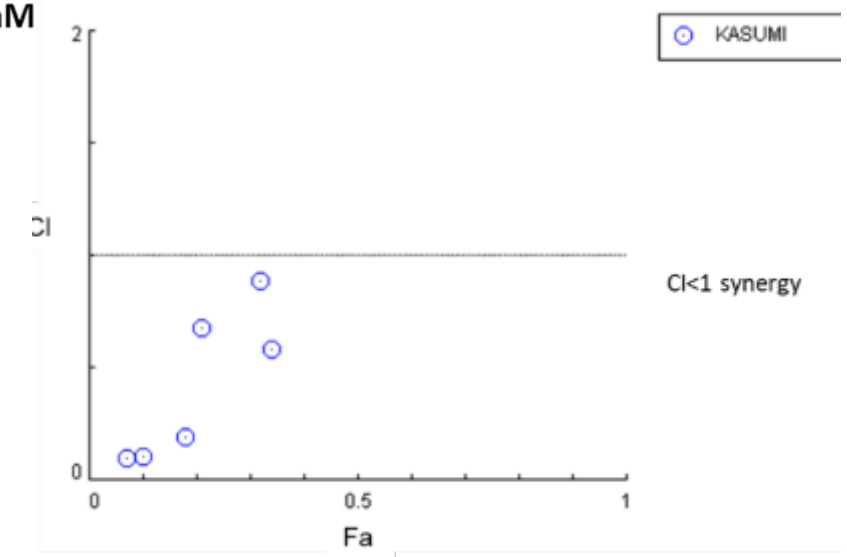
Preclinical Plogo (aka CYC140) + Aza Activity in AML



Cell lines	CYC IC50	AZA IC50
p53 mut KASUMI	112 nM	415 nM

Dose cyc (nM)	Dose aza (nM)	Effect	CI
112.0	100.0	0.34	0.58177 ◀
112.0	500.0	0.32	0.88934
112.0	1000.0	0.21	0.67775 ◀
30.0	415.0	0.18	0.19355 ◀
50.0	415.0	0.1	0.10447 ◀
100.0	415.0	0.07	0.09959 ◀



Data on file.

◀ Synergy

Milestone Momentum

- **Fadra** initial Phase 2 data in patients with CDKN2A/B abnormalities 2H 24
- Begin lymphoma cohort 2H 24
- Complete tablet manufacture and validation 2H 24
- **Plogo** alternative salt formulation clinical supply availability

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** Subject to available capital.*

Thank You

Cyclacel Pharmaceuticals, Inc.

200 Connell Drive #1500
Berkeley Heights, NJ 07922

Contact: ir@cyclacel.com
+1 (908) 517 7330