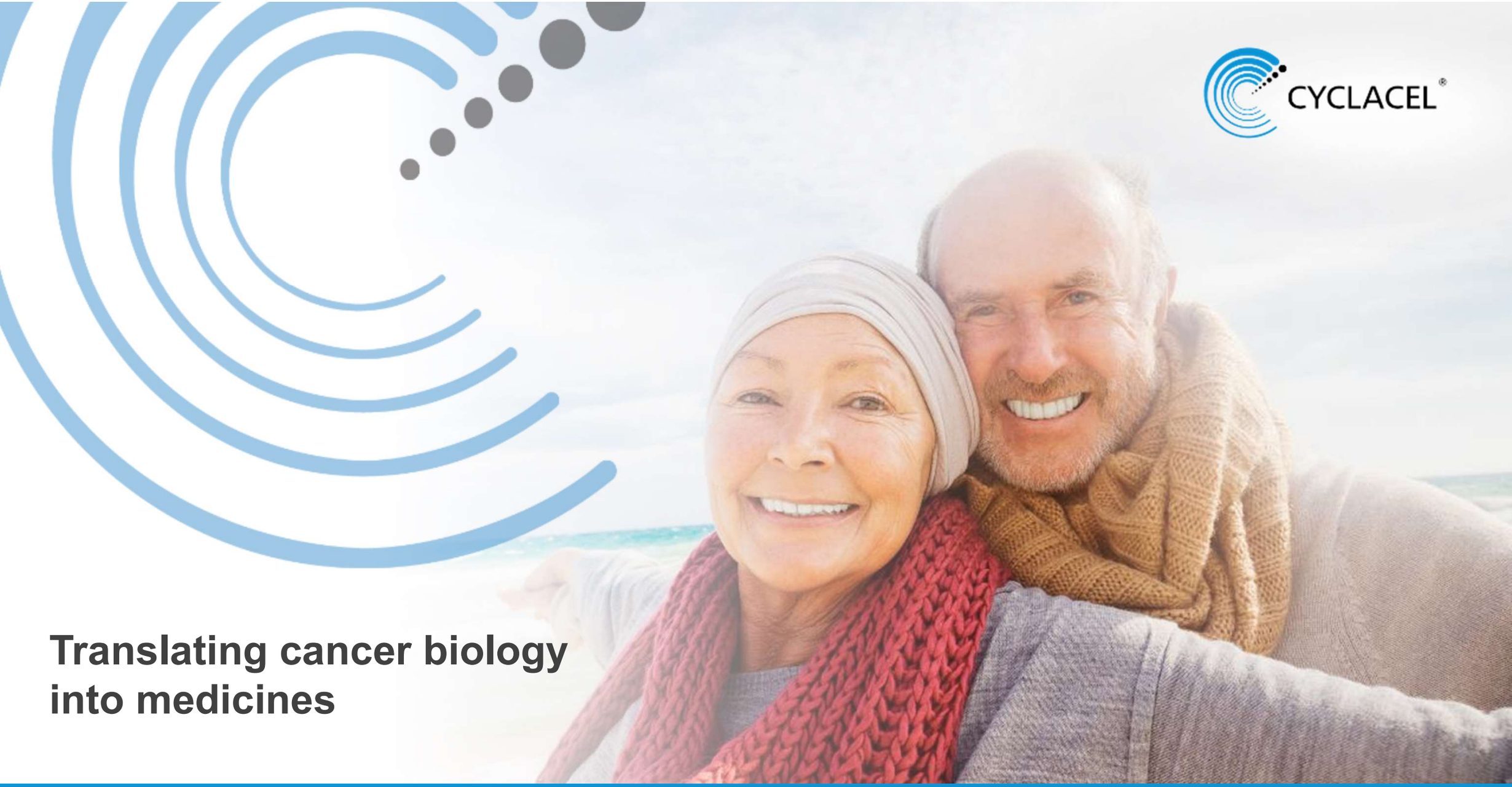

Translating cancer biology into medicines

Cyclacel Pharmaceuticals, Inc. (CYCC) APRIL 2024

Disclaimer

This presentation contains certain forward-looking statements that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, the efficacy, safety and intended utilization of Cyclacel's product candidates, the conduct and results of future clinical trials, plans regarding regulatory filings, future research and clinical trials and plans regarding partnering activities. Factors that may cause actual results to differ materially include the risk that product candidates that appeared promising in early research and clinical trials do not demonstrate safety and/or efficacy in larger-scale or later clinical trials, trials may have difficulty enrolling patients, Cyclacel may not obtain approval to market its product candidates, the risks associated with reliance on outside financing to meet capital requirements, and the risks associated with reliance on collaborative partners for further clinical trials, development and commercialization of product candidates. You are urged to consider statements that include the words "may," "will," "would," "could," "should," "believes," "estimates," "projects," "potential," "expects," "plans," "anticipates," "intends," "continues," "forecast," "designed," "goal," or the negative of those words or other comparable words to be uncertain and forward-looking. For a further list and description of the risks and uncertainties the Company faces, please refer to our most recent Annual Report on Form 10-K and other periodic and other filings we file with the Securities and Exchange Commission and are available at www.sec.gov. Such forward-looking statements are current only as of the date they are made, and we assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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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

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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.

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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
16 oral *065-101*	Cholangio-carcinoma	**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

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Data on file. Pt 62 unmonitored data. Mutational status with CDKN2A/B alterations: in oral study: 5/21, in IV study: 6/20 patients. Pt 20 i.v. pancreaticobiliary; 192 mg/m2; 1 C only) CDKN2A loss.

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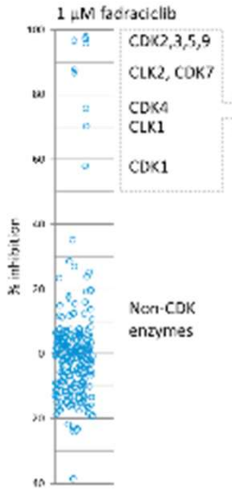
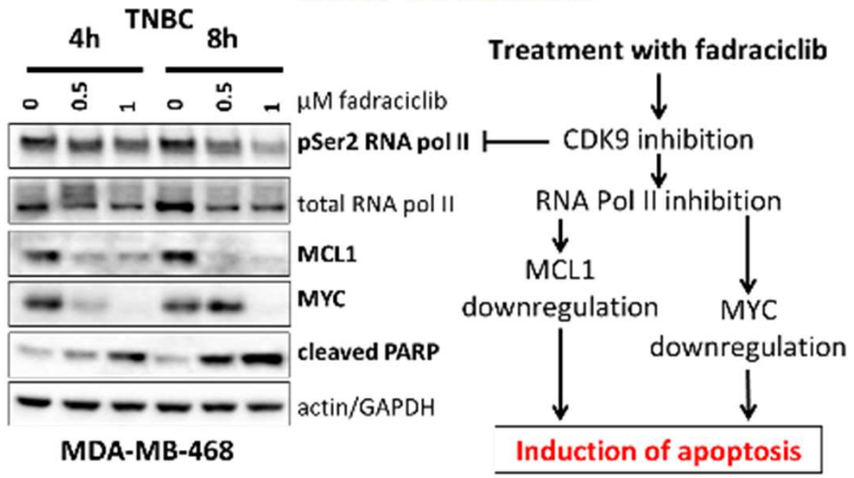
Fadra – Novel and Potent CDK2 and CDK9 inhibitor

Kinase Profile

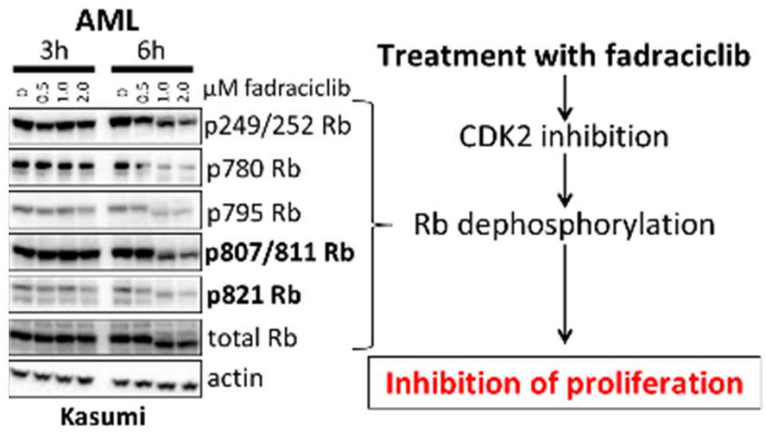


Enzyme	Fadraciclib IC_{50} (nM)	Fold Diff. to CDK2
CDK2	**4.5**	**1.0**
CDK5	**20.5**	**4.6**
CDK9	**26.2**	**5.8**
CDK3	**28.9**	**6.4**
CDK7	193	43
CDK4	232	52
CLK2	252	56
CLK1	549	122
CDK1	578	128

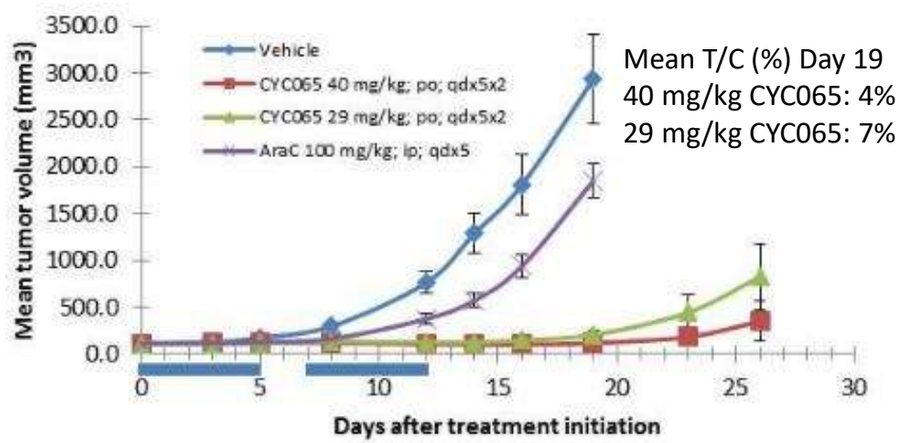
CDK9 inhibition



CDK2 inhibition

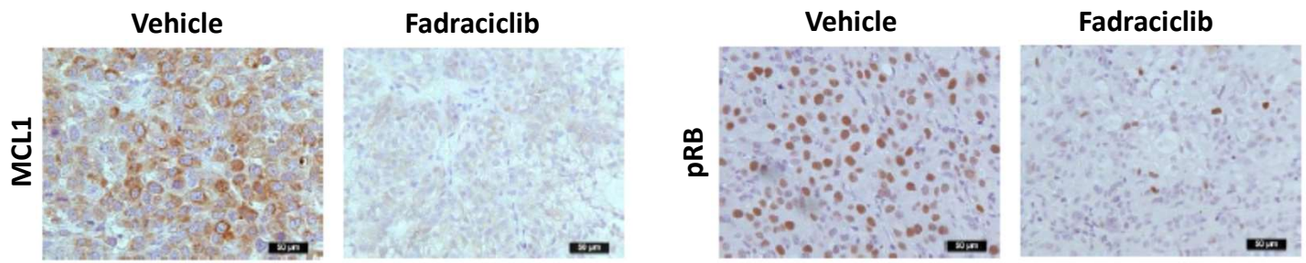


EOL-1 (KTM2A-PTD, CDKN2A/B Loss) AML xenograft



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



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

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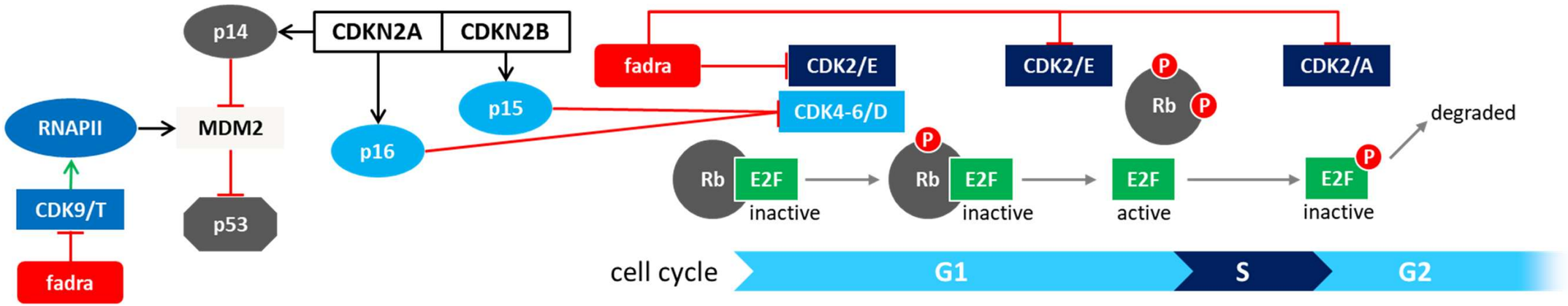
CDKN2A/B and Fadra MoA



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.*

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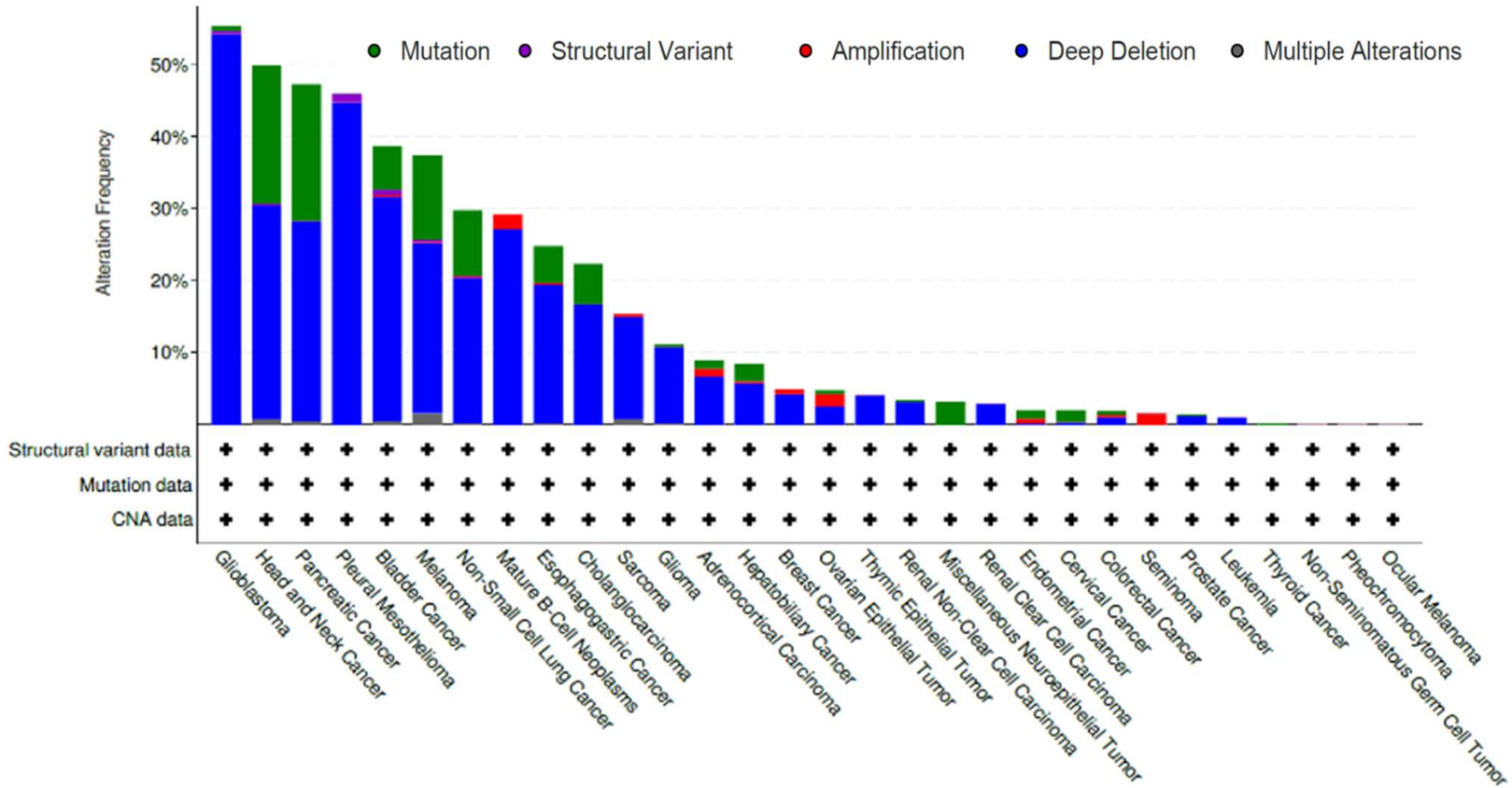
CDKN2A Alterations



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

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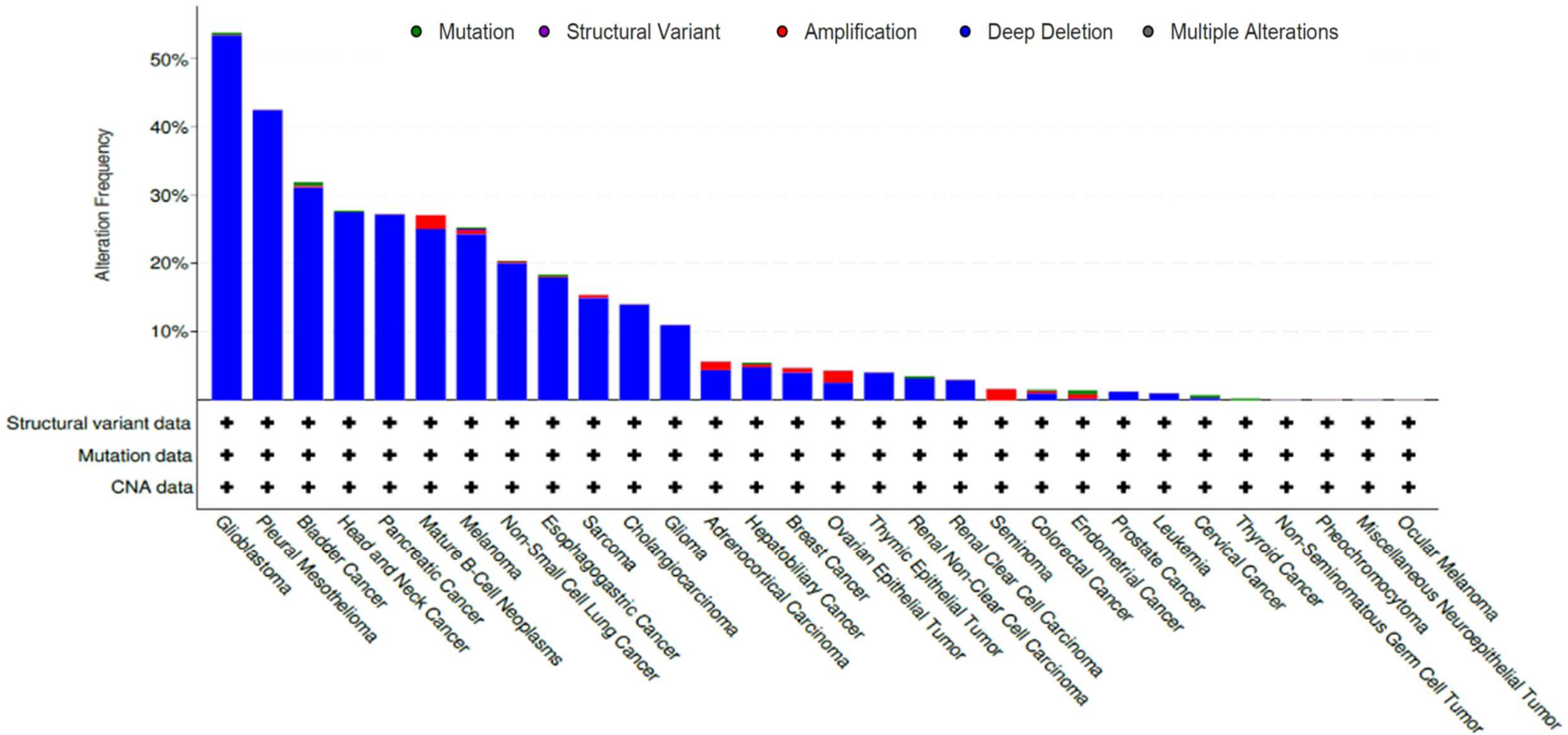
CDKN2B Alterations



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

cBioportal, dl 23OCT23.

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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

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

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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.

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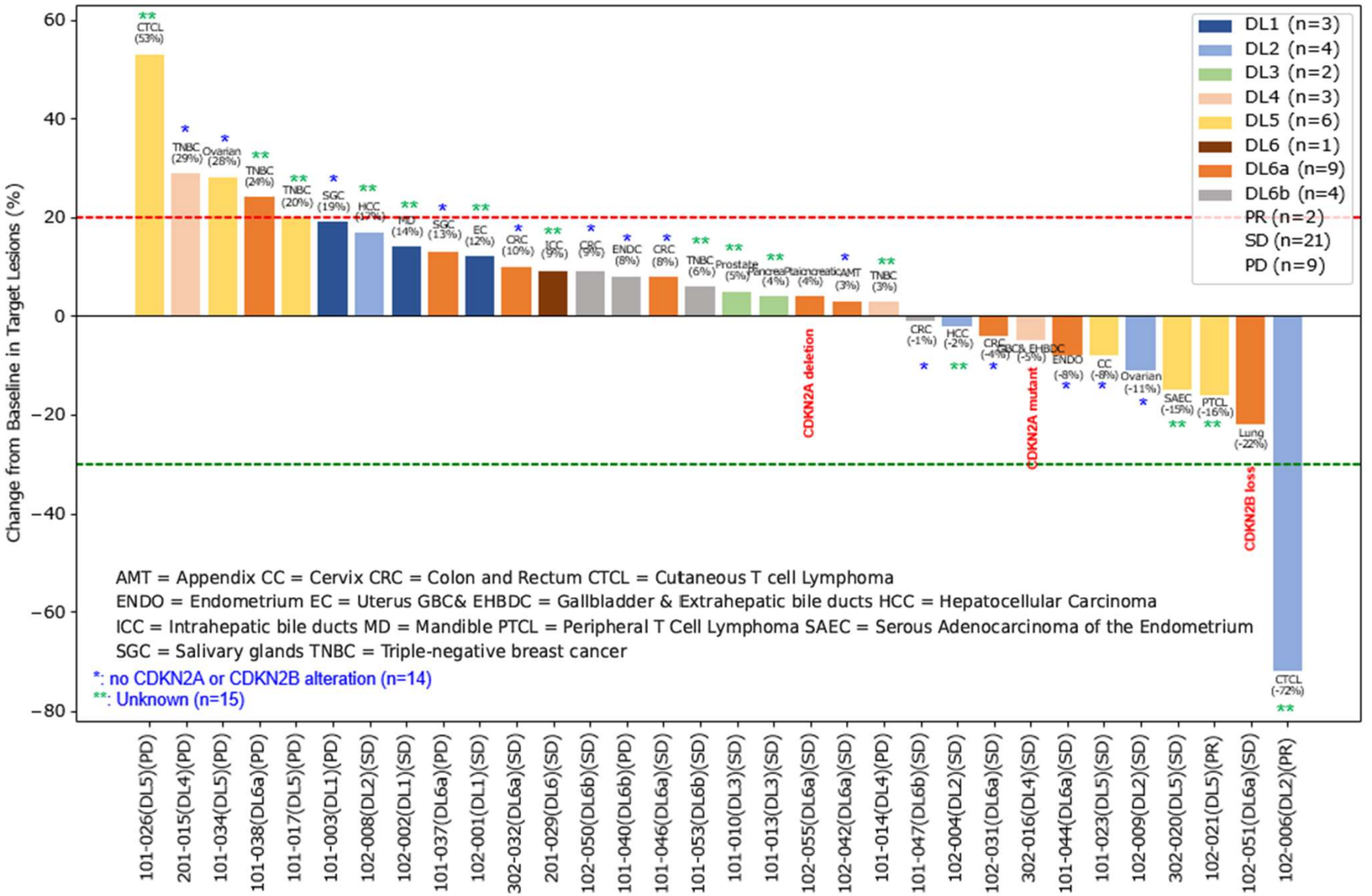
Oral Fadra 065-101 Response *(all comer, n=32, as of 31JAN24)*



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. Data on file as of 31JAN24.

**Tumor assessments done at 4 weeks post-treatment and every 8 weeks thereafter.*

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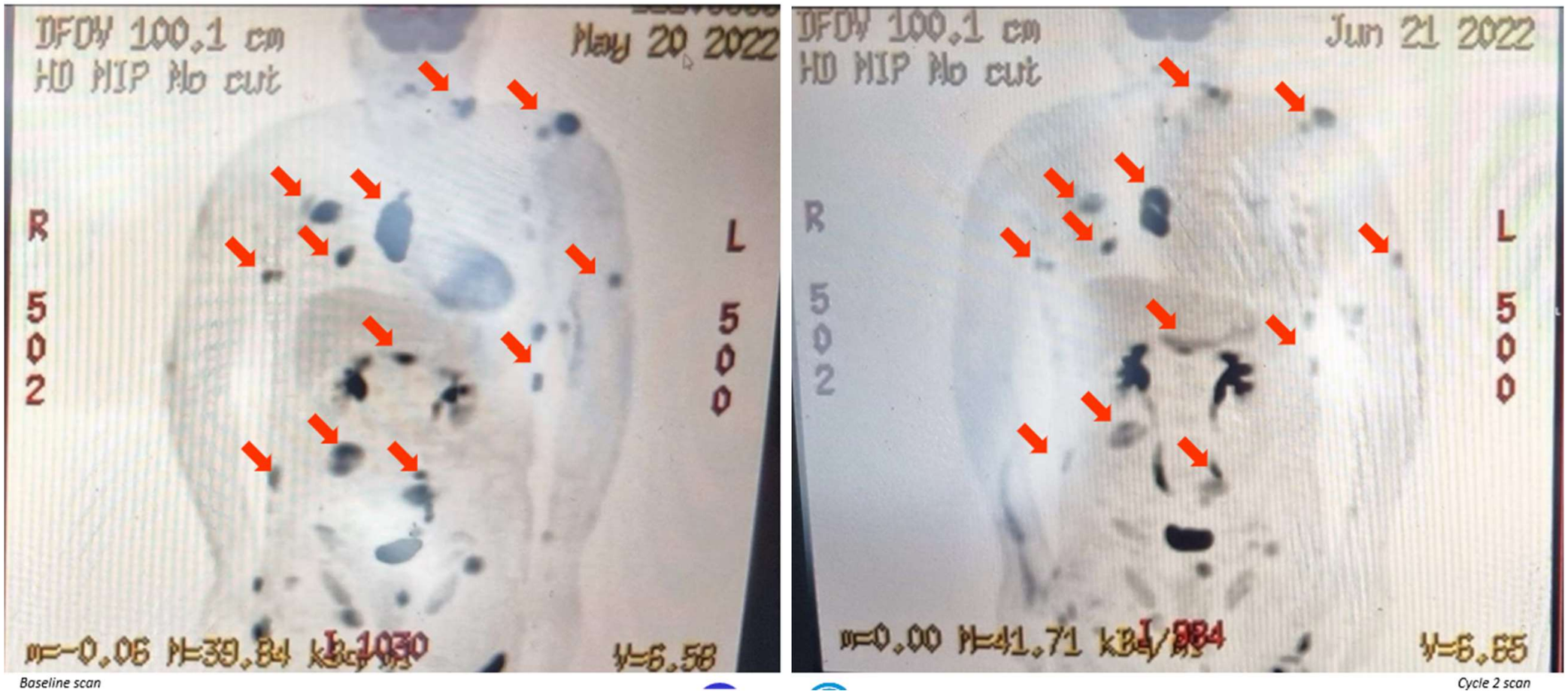
PR in angioimmunoblastic PTCL pt. *(oral 065-101, 1st cycle DL5)*



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.*

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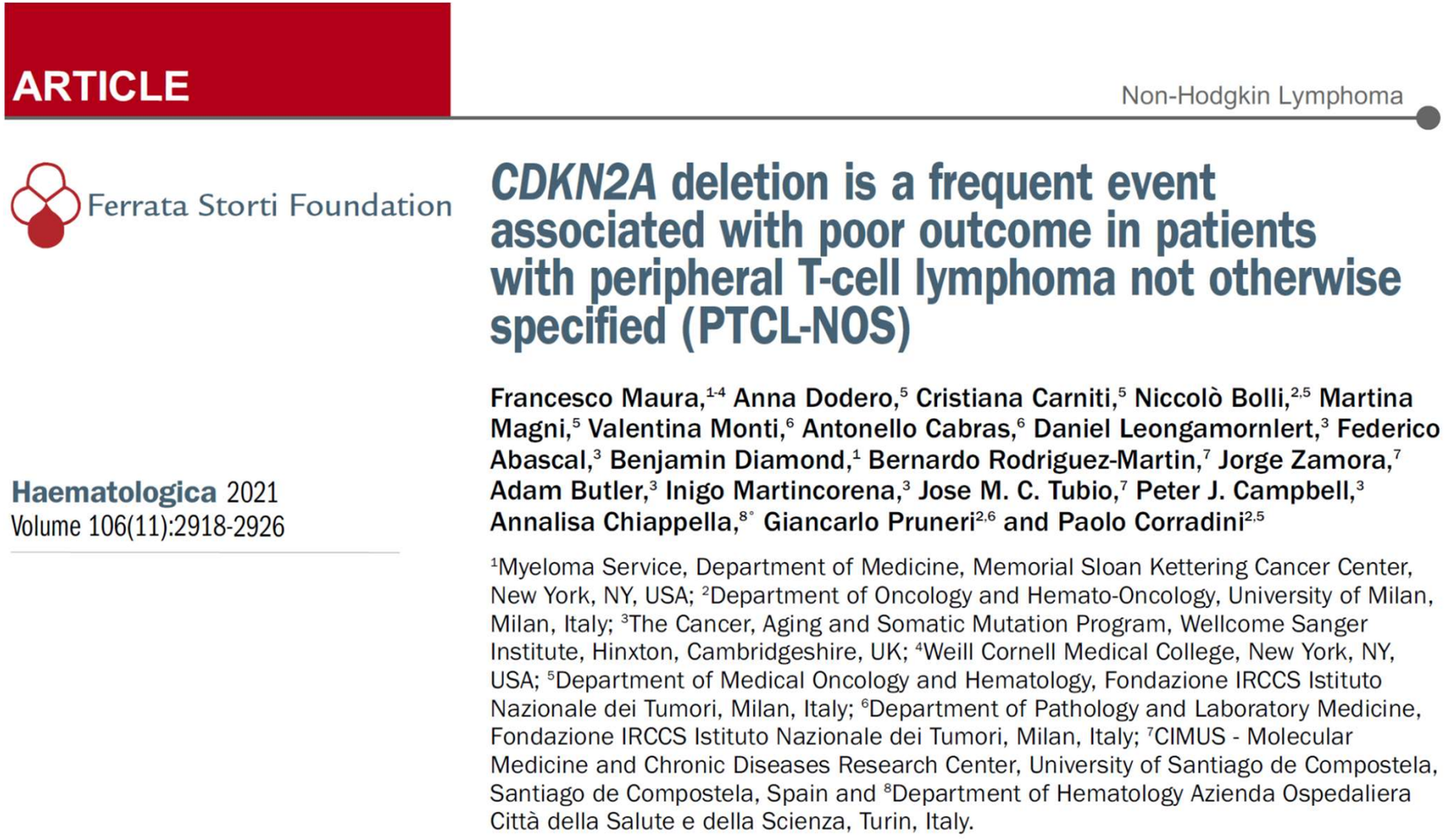
CDKN2A deletion in T Cell Lymphoma

Incidence of CDKN2A deletions was 46%.[1]



ARTICLE

Non-Hodgkin Lymphoma

Ferrata Storti Foundation

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.

Haematologica 2021
Volume 106(11):2918-2926

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

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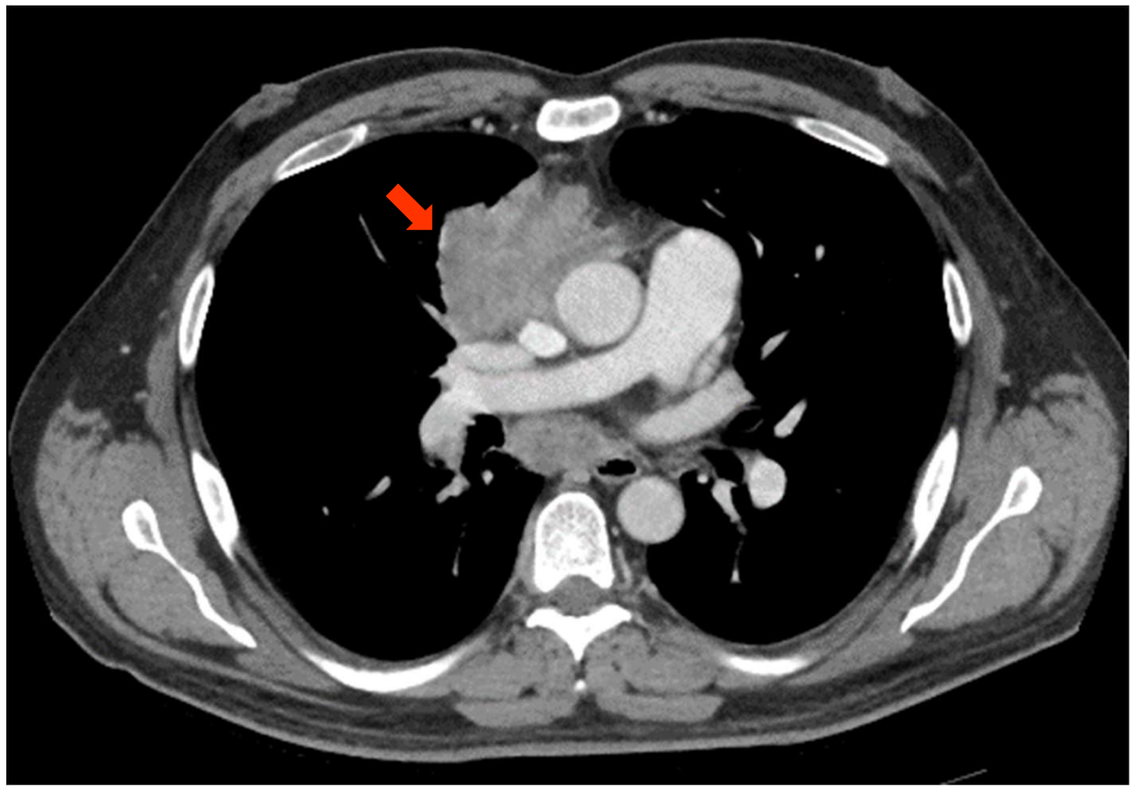
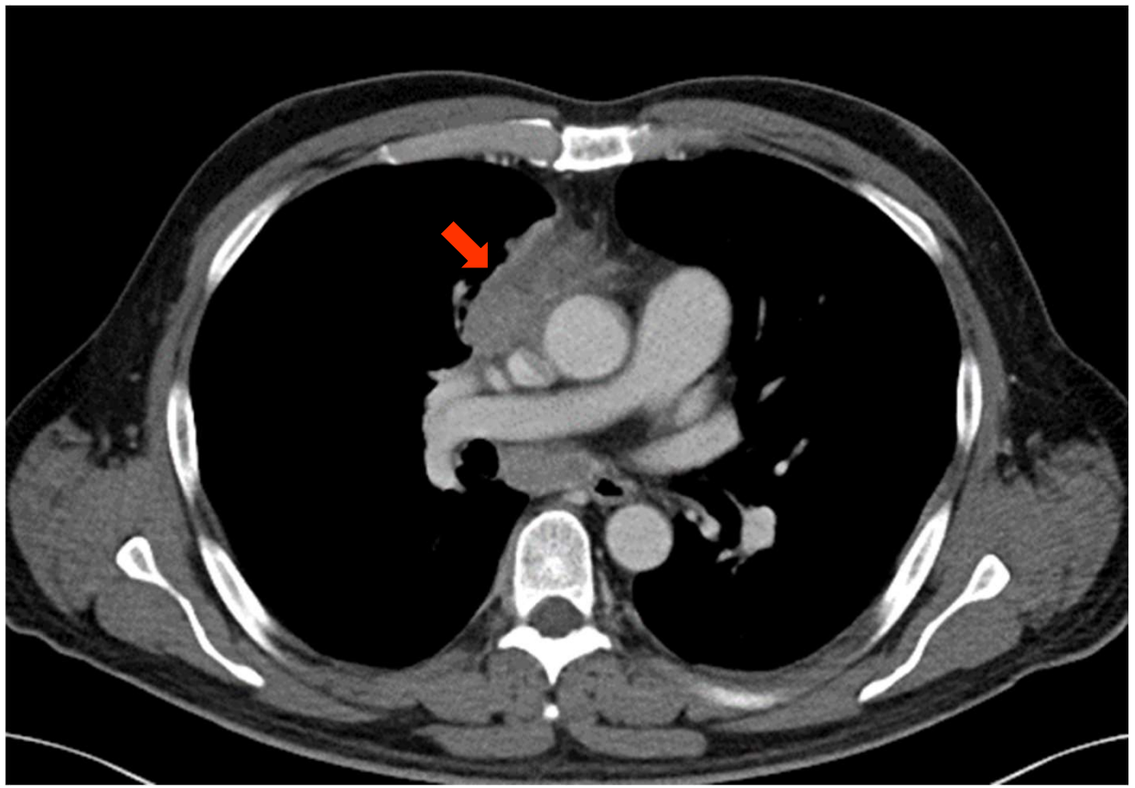
Squamous NSCLC patient *(oral 065-101, 1 cycle DL6a)*



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

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

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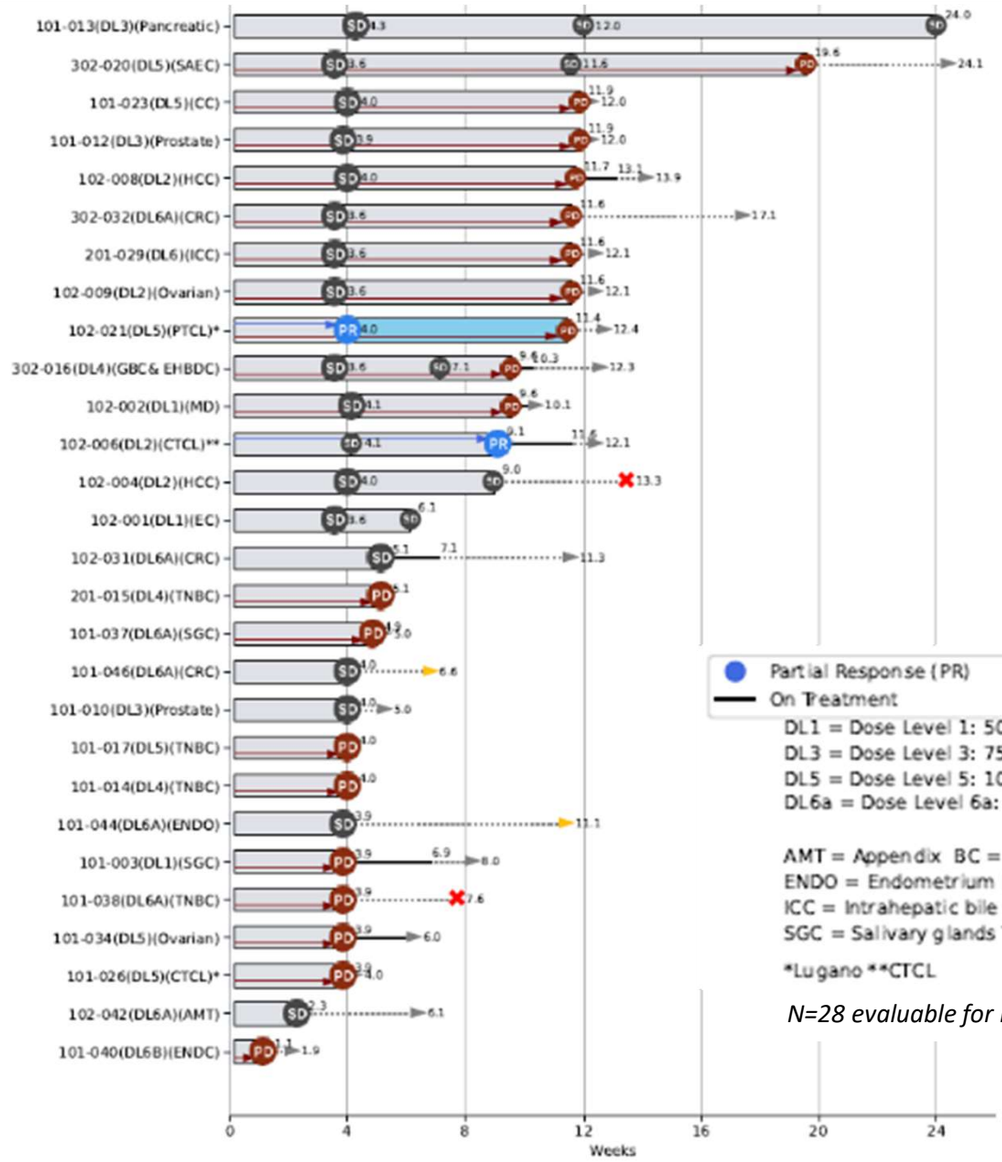
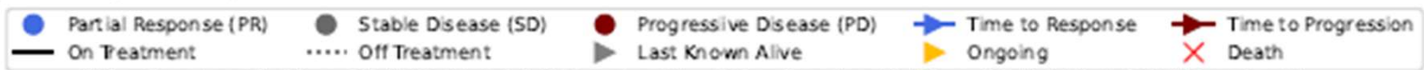
Fadra Oral 065-101 Swimmers Plot *(dose escalation part)*





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) DL6 = Dose Level 6: 150mg, BID M-F, Week 1-4 (1500 mg/week)
DL6a = Dose Level 6a: 125mg, BID M-F, Week 1-4 (1250 mg/week) DL6b = Dose Level 6b: 150mg, QD, Week 1-4 (1050 mg/week)

AMT = Appendix BC = Breast CC = Cervix CRC = Colon and Rectum CTCL = Cutaneous T cell lymphoma ENDC = Endometrioid
ENDO = Endometrium EC = Uterus GBC& EHBDC = Gallbladder & Extrahepatic bile ducts HCC = Hepatocellular Carcinoma
ICC = Intrahepatic bile ducts MD = Mandible PTCL = Peripheral T Cell Lymphoma SAEC = Serous Adenocarcinoma of the Endometrium
SGC = Salivary glands TNBC = Triple-negative breast cancer

*Lugano **CTCL

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

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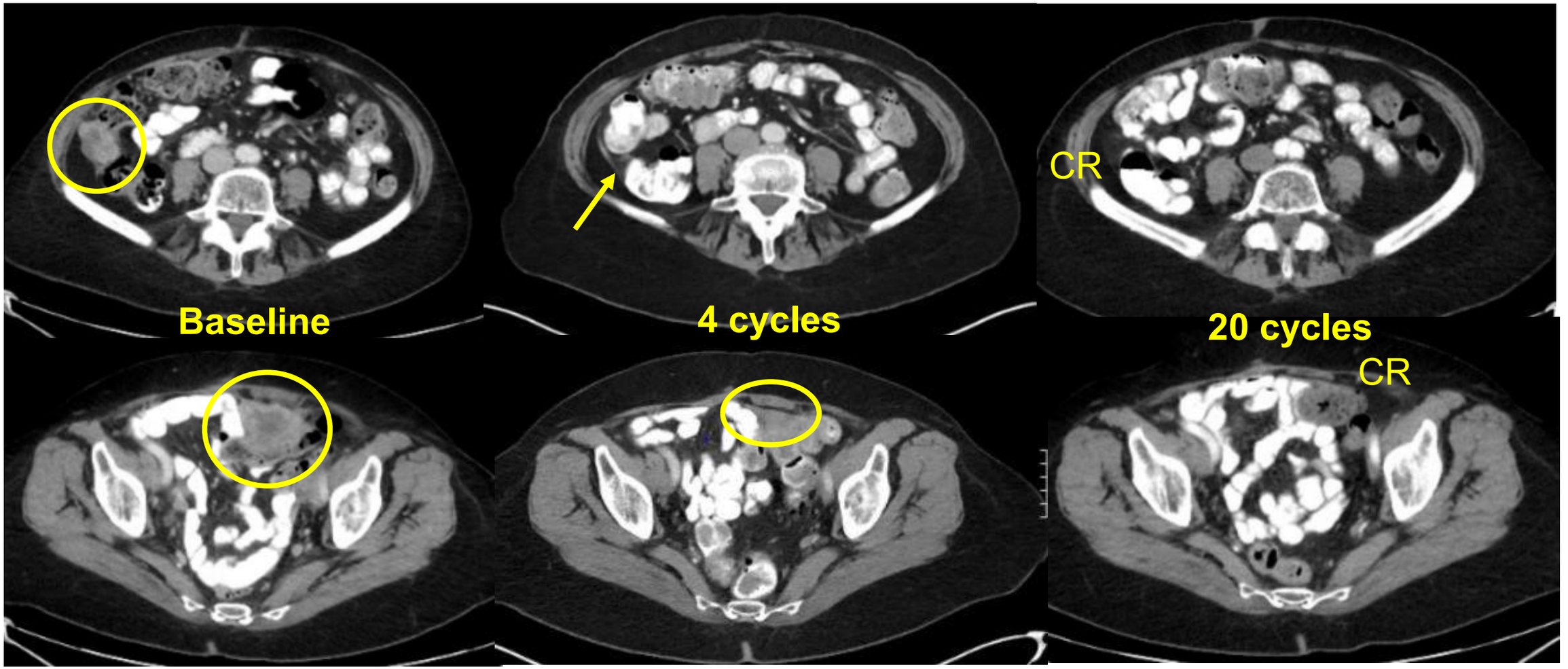
PR then CR 065-01 Part 2 IV Endometrial Pt *(CDKN2A, CDKN2B and MTAP loss)*



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

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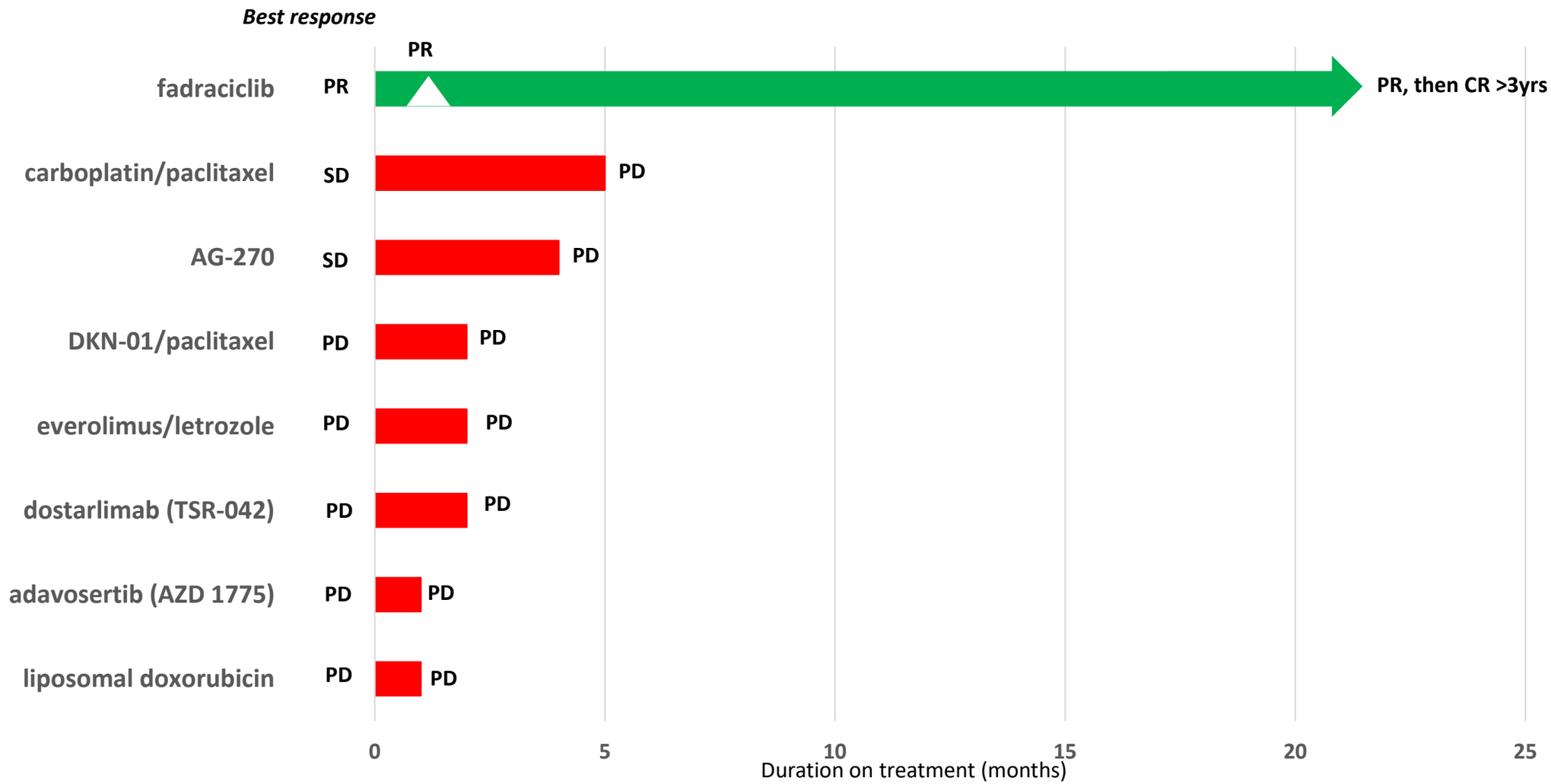
Endometrial Patient History 065-01 Part 2 IV



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

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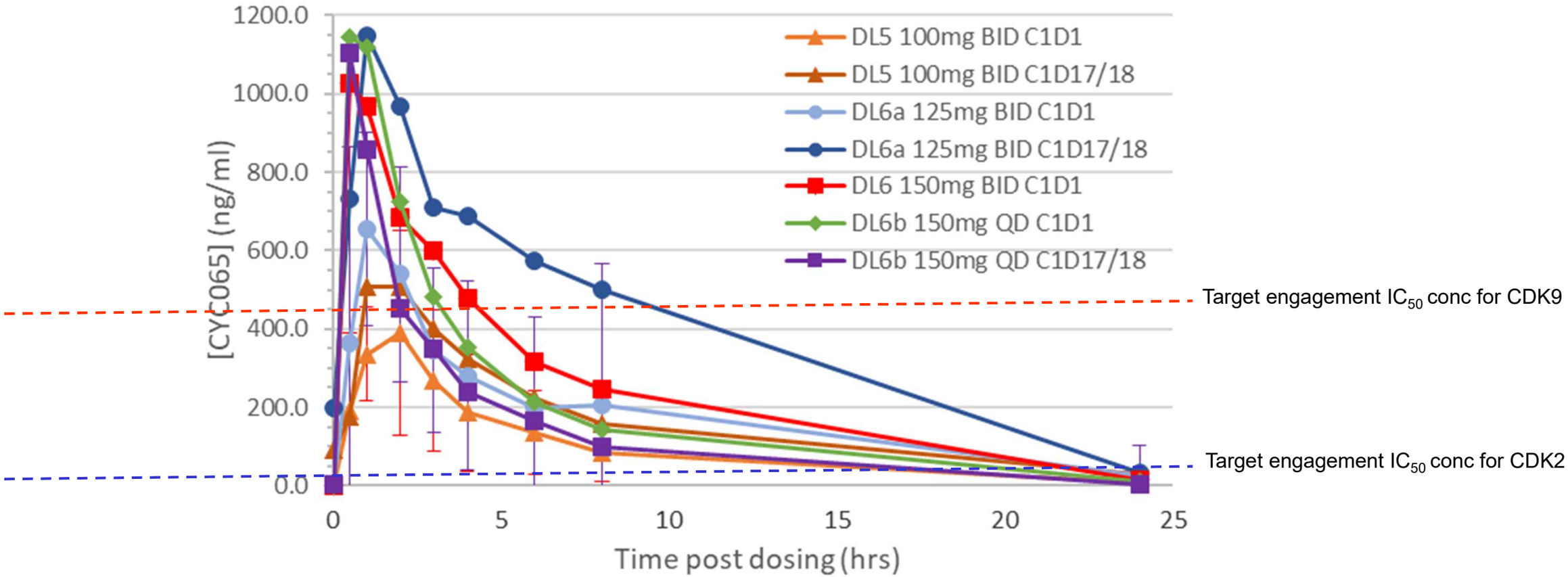
Dose Proportional PK with CDK2 and 9 Coverage at Higher Dose Levels



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

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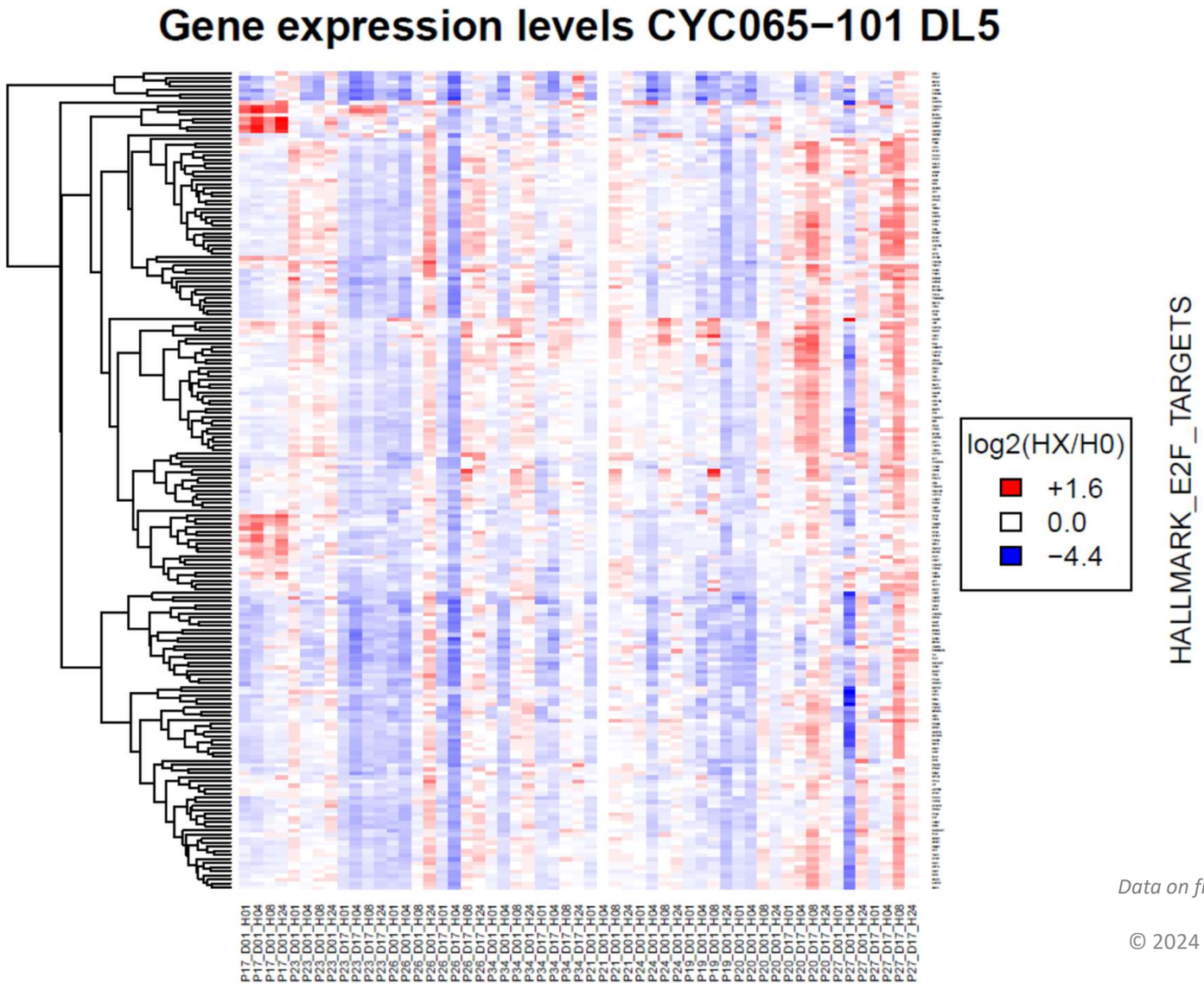
Fadra Suppresses E2F (CDK2 dependent) DL5 Phase 1 Patients



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

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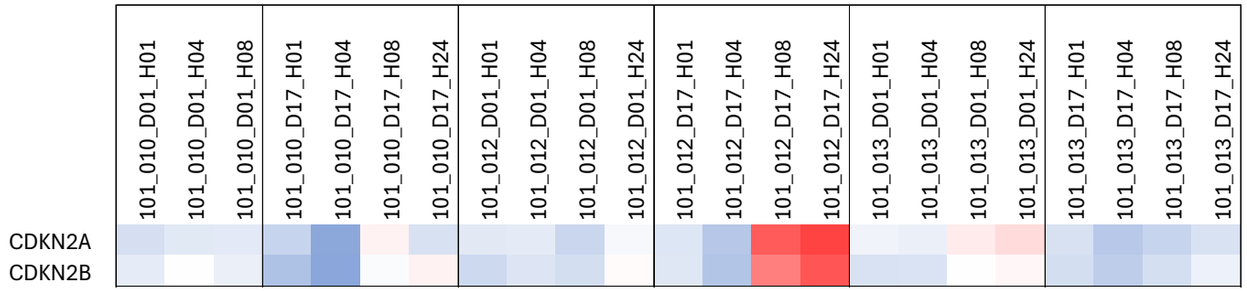
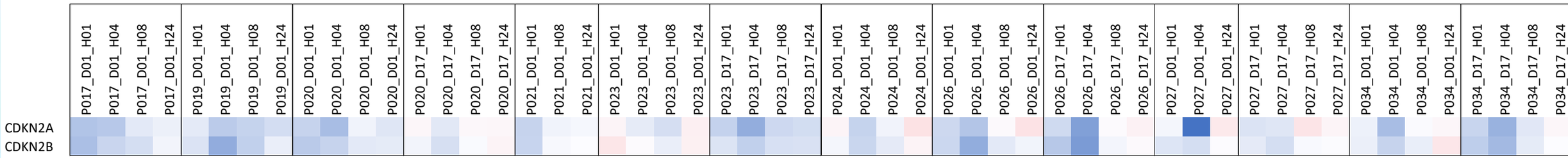
Fadra Suppresses CDKN2A/B Transcription in Patients

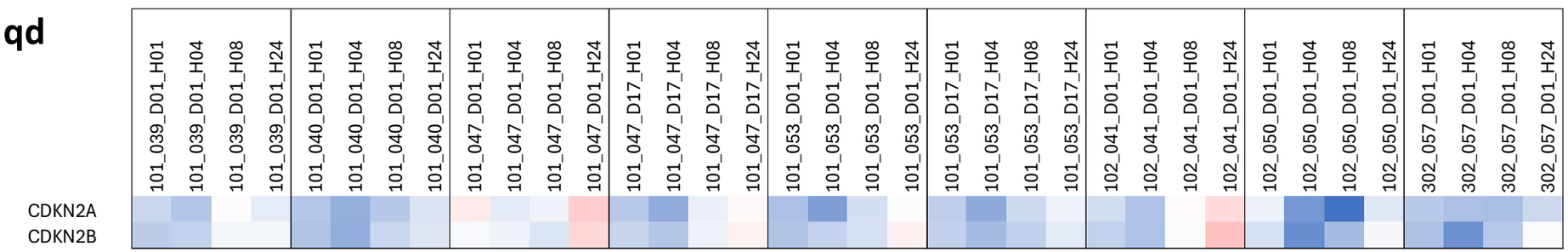
DL2: 50 mg bid



DL5: 100 mg bid



DL6b: 150 mg qd



Data on file. RNAseq transcript data.

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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

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.

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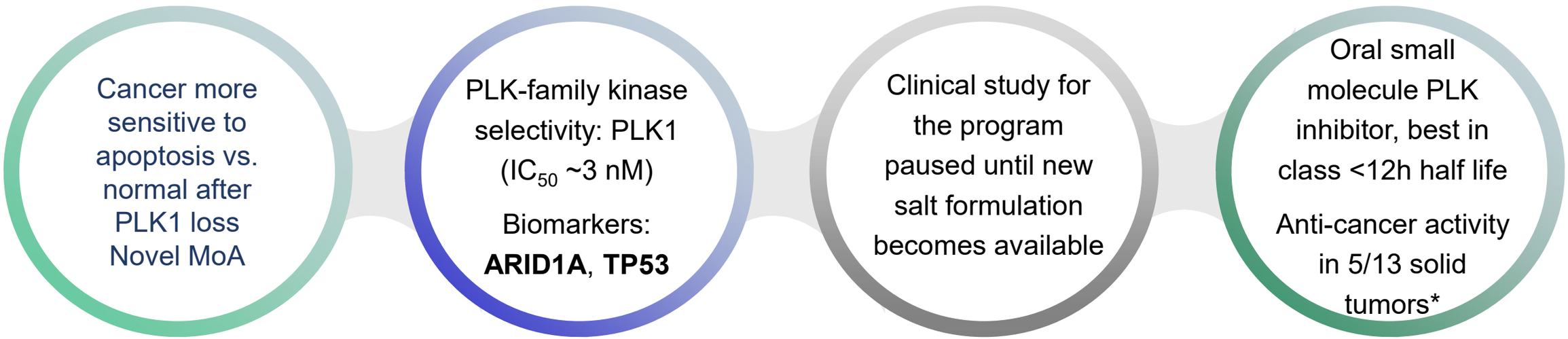
Plogosertib (CYC140) Next Gen PLK1 inhibitor



Novel mechanism with a unique **mutational** strategy

Targeting ARID1A and TP53 Mutated Cancers

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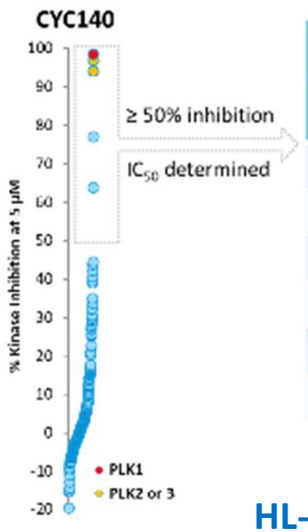
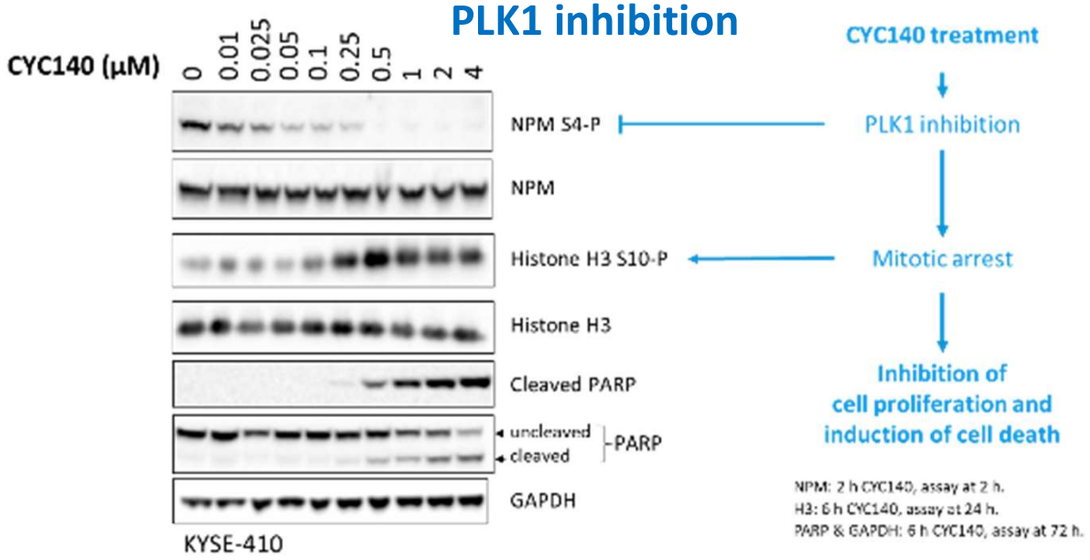
Plogo Preclinical Activity

Kinase Profile

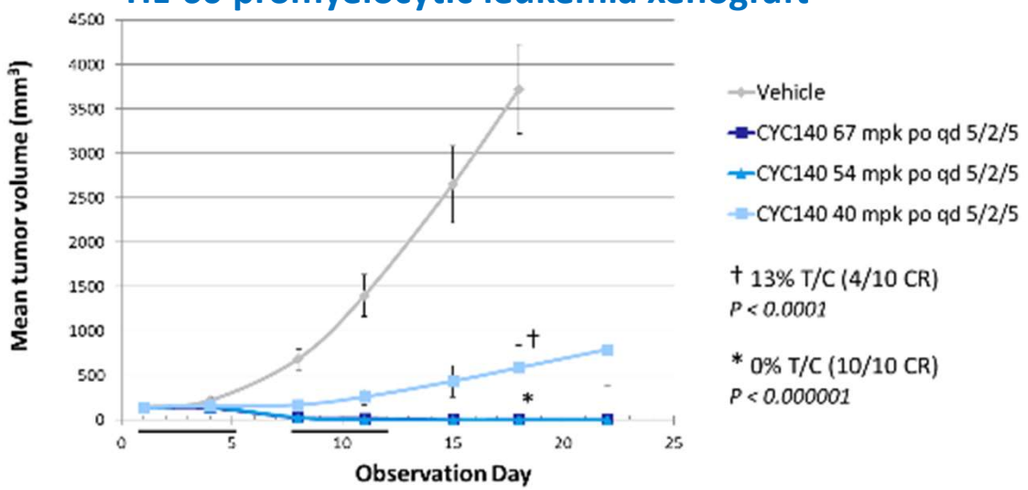


Kinase	CYC140 IC_{50} (nM)	PLK1 Selectivity (fold)
PLK1	2.7	1
PLK2	155	58
EIF2AK3	292	109
PLK3	297	112
CaMK2δ	1630	612
DAPK1	2860	1074

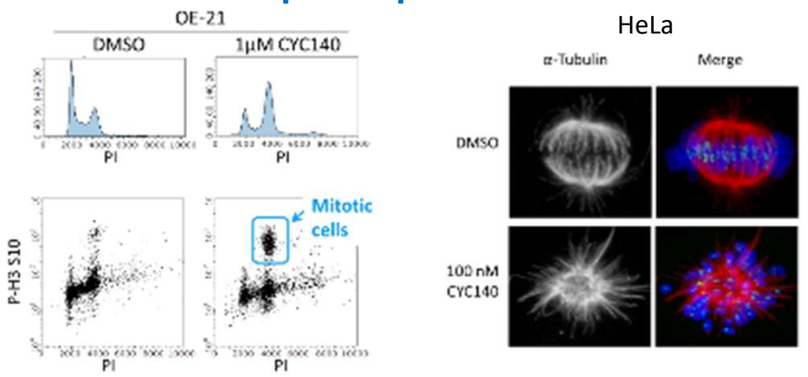
PLK1 inhibition



HL-60 promyelocytic leukemia xenograft



CYC140 increases mitotic cell number and induces monopolar spindle formation



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

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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*

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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.

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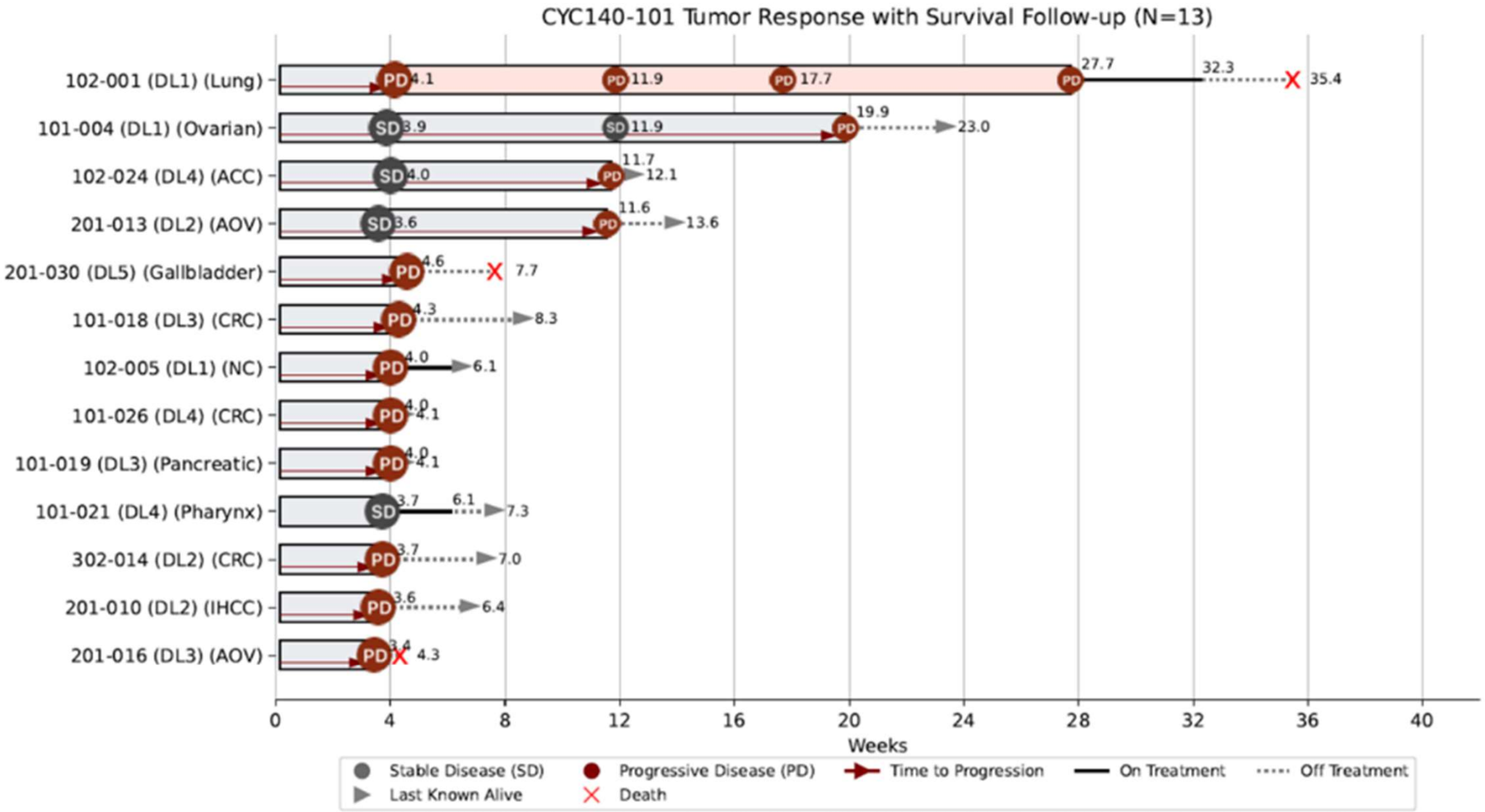
Plogo Oral 140-101 DL1-4 Swimmers Plot *(dose escalation ongoing)*



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

Data on file.

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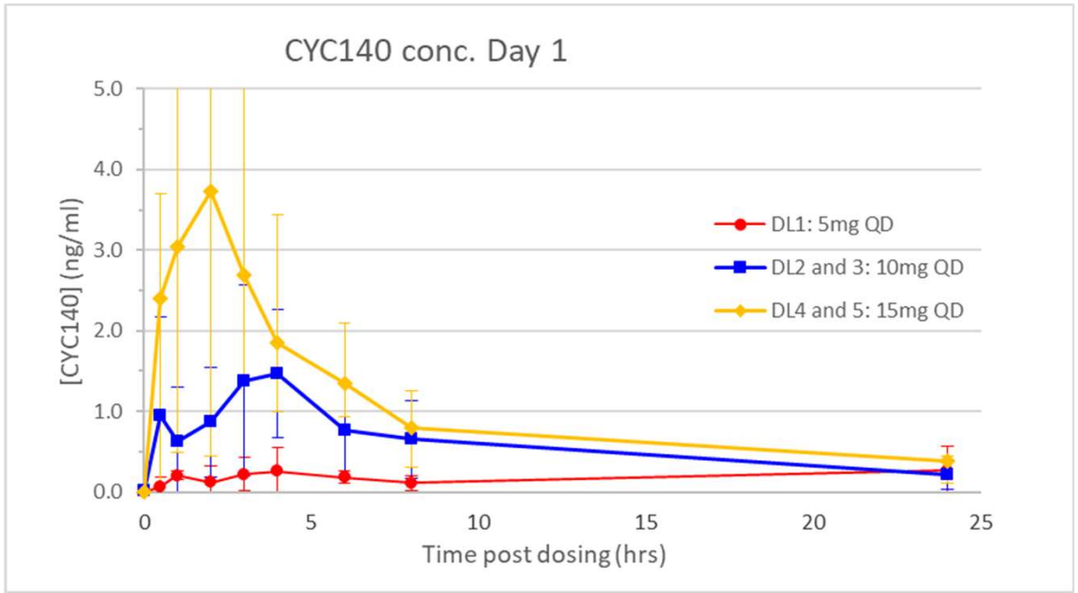
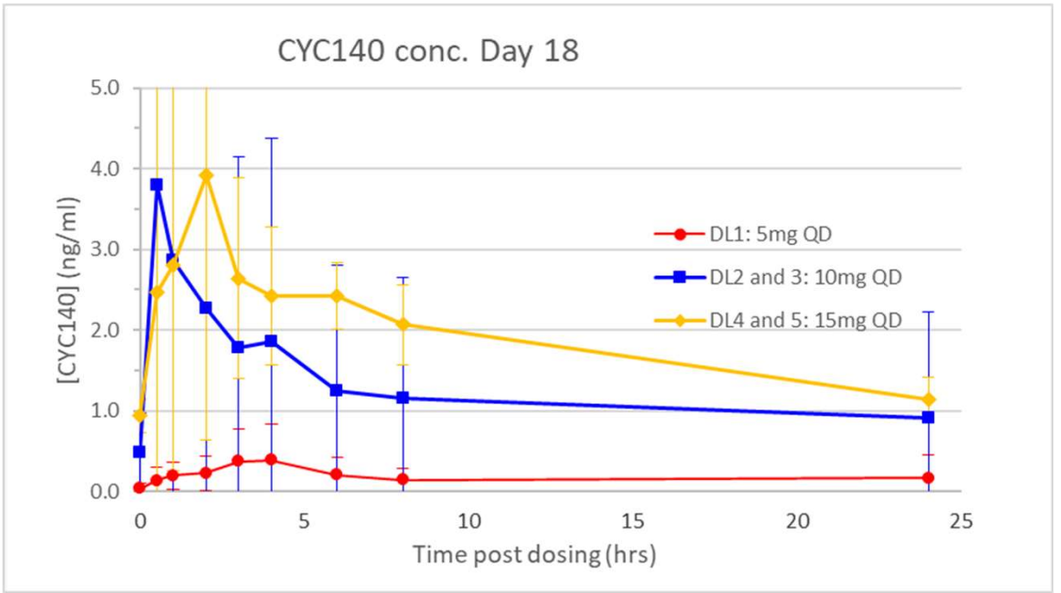
Mean (±SD) Plasma Plogo Concentration-Time Plot C1D1 & C1D18

Day 1



Day 18



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

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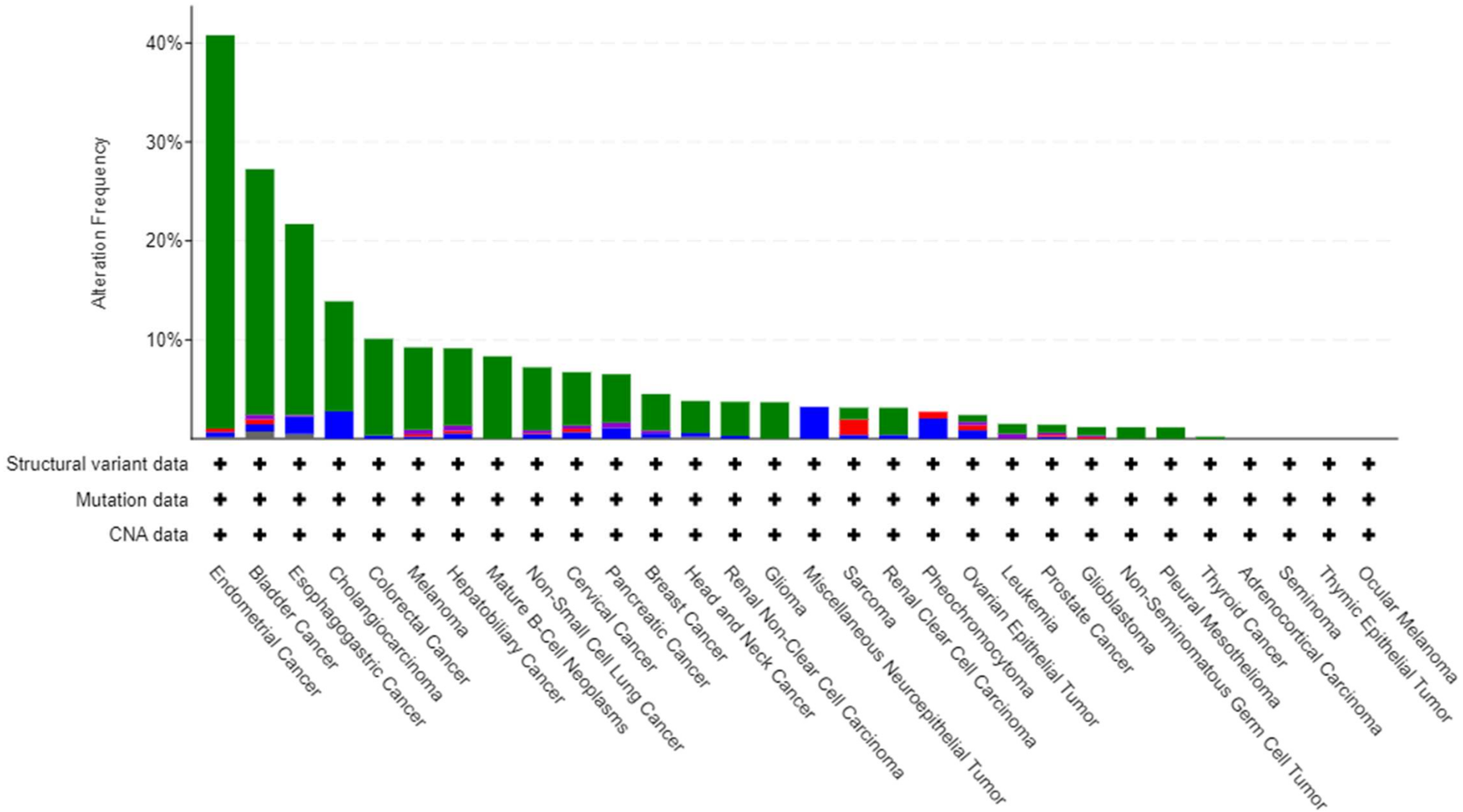
ARID1A Modifications



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

cBioportal, dl 23OCT23.

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TP53 Mutated Unmet Need

1L AML Standard of Care: venetoclax + azacitidine

TP53 mutated patients do not benefit from ven + aza; 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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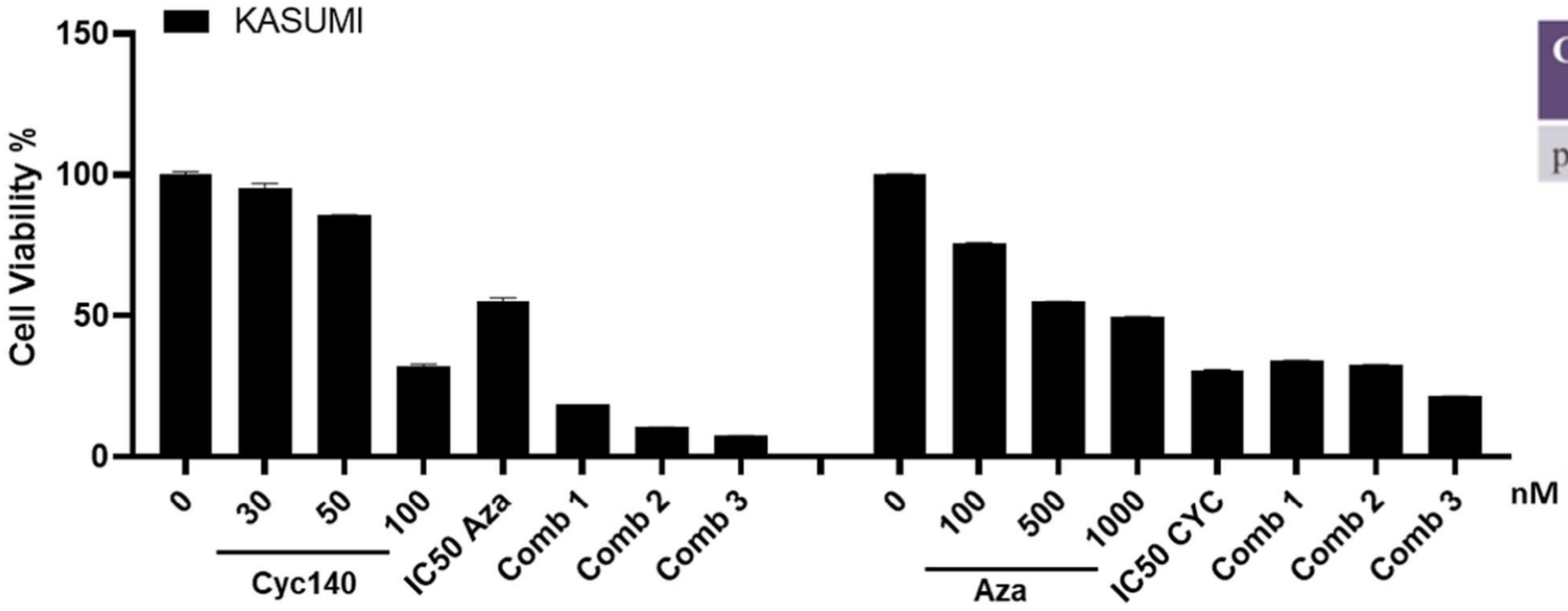
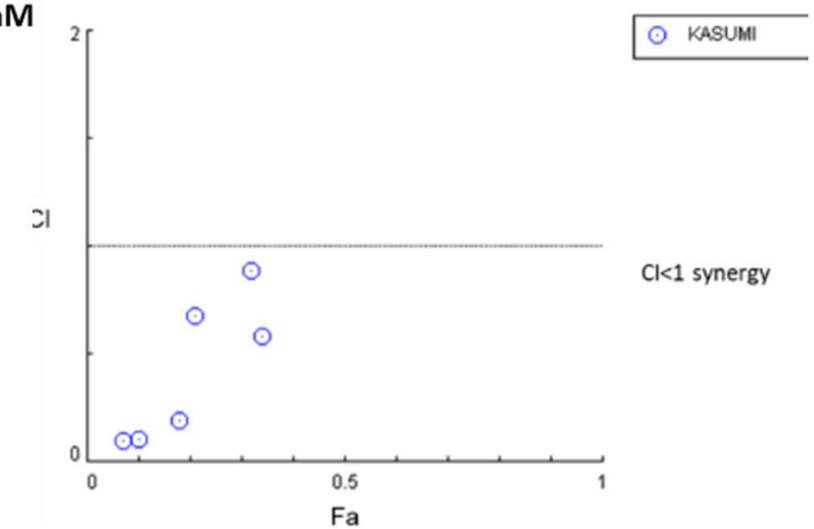
Preclinical Plogo (aka CYC140) + Aza Activity in AML



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

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Plogo Potentially “Only-in-Class” Mutational Strategy

Plogo enables **chromatin accessibility** at low concentrations

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, and AML.

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Data on file.

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Milestone Momentum

- **Fadra** Phase 1 final data to include PK, PD, safety and activity data 1H 2024
- ✓ Determine RP2D
- Begin Phase 2 solid tumor Proof of Concept 1H 2024
  - Two cohorts: biomarker-driven CDKN2A/B abnormalities and T-cell lymphoma
- Initial Phase 2 PoC data from disease specific cohorts* 2H 2024
- Complete tablet manufacture and validation 2H 2024
- **Plogo** alternative salt formulation clinical supply availability

CYCLACEL

** Subject to available capital.*

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Thank You

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