Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of Fadraciclib (CYC065), a Cyclin-Dependent Kinase Inhibitor, in Patients with Advanced Cancers (NCT02552953)

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Disclosure Information

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Presented by: Khanh Do, M.D.

The presenter has no financial relationships to disclose.
This presentation will not be discussing off-label use.

Employees of Cyclacel Ltd:

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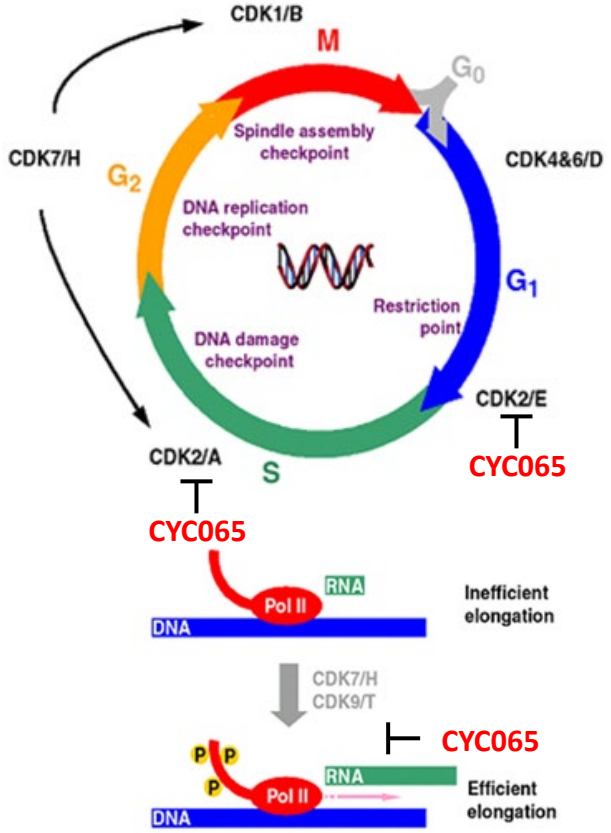
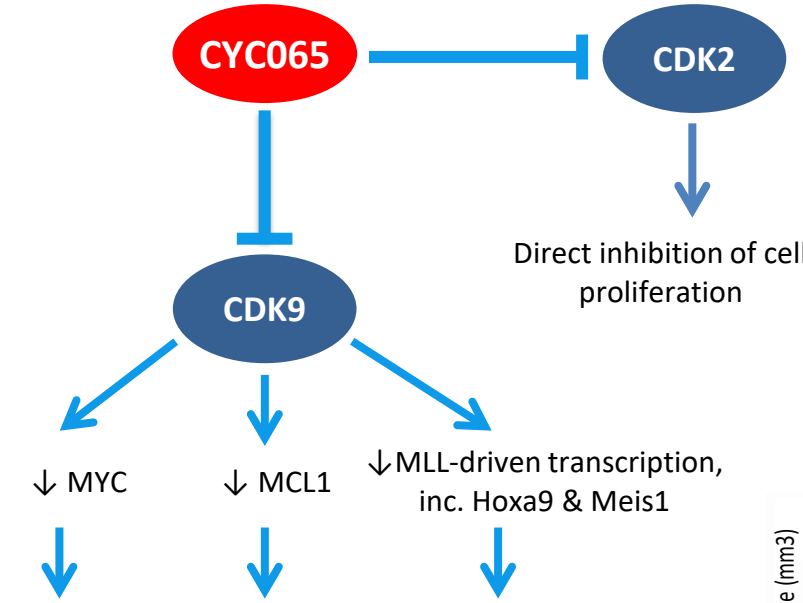
Overview: Cyclin Dependent Kinases



- Cell cycle dysregulation is a hallmark of cancer
- Cyclins/cyclin dependent kinases (CDKs) are involved in regulation of the cell cycle: CDK 1, 2, 4, 6, 7 (CAK)
- CDK 7, 8, 9, and 12 also regulate gene transcription through phosphorylation of RNA Pol II

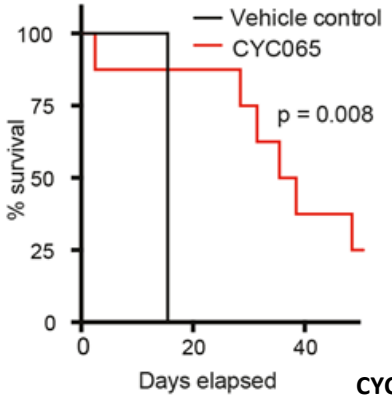
- **Fadraciclib (CYC065)** is a 2nd generation aminopurine inhibitor of CDK2 and CDK9
  - *In vitro* kinase potency (IC_{50}) :
    CDK2 = 5 nM; CDK9 = 26 nM

Preclinical Overview (Key targets: MCL1, MYC, cyclin E, MLL)

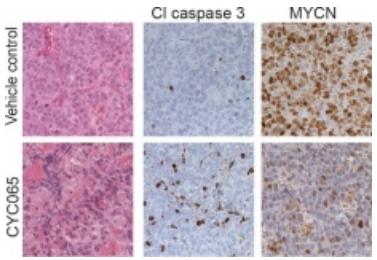


Direct inhibition of cell proliferation

Apoptosis of tumors that are dependent on CDK9-mediated transcription of MCL1, MYC or MLL-target genes

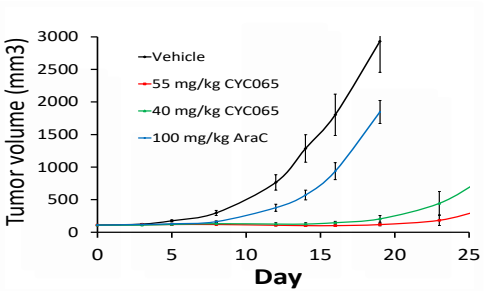


MYCN amplified Neuroblastoma

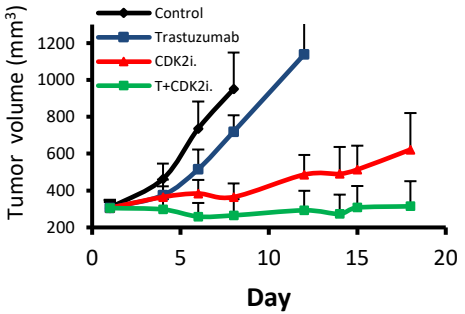


CYC065: 50 mg/kg po 5 days/week x 2

MLLr - AML



Cyclin E amp - resistant BC



CYC065: 22.5 mg/kg po qd

Source: Poon et al. 2016; Saladino et al. 2015; Scaltriti et al. 2011.

Study Objectives and Design

Primary Objective:

- To determine MTD and recommended phase 2 dose (RP2D)

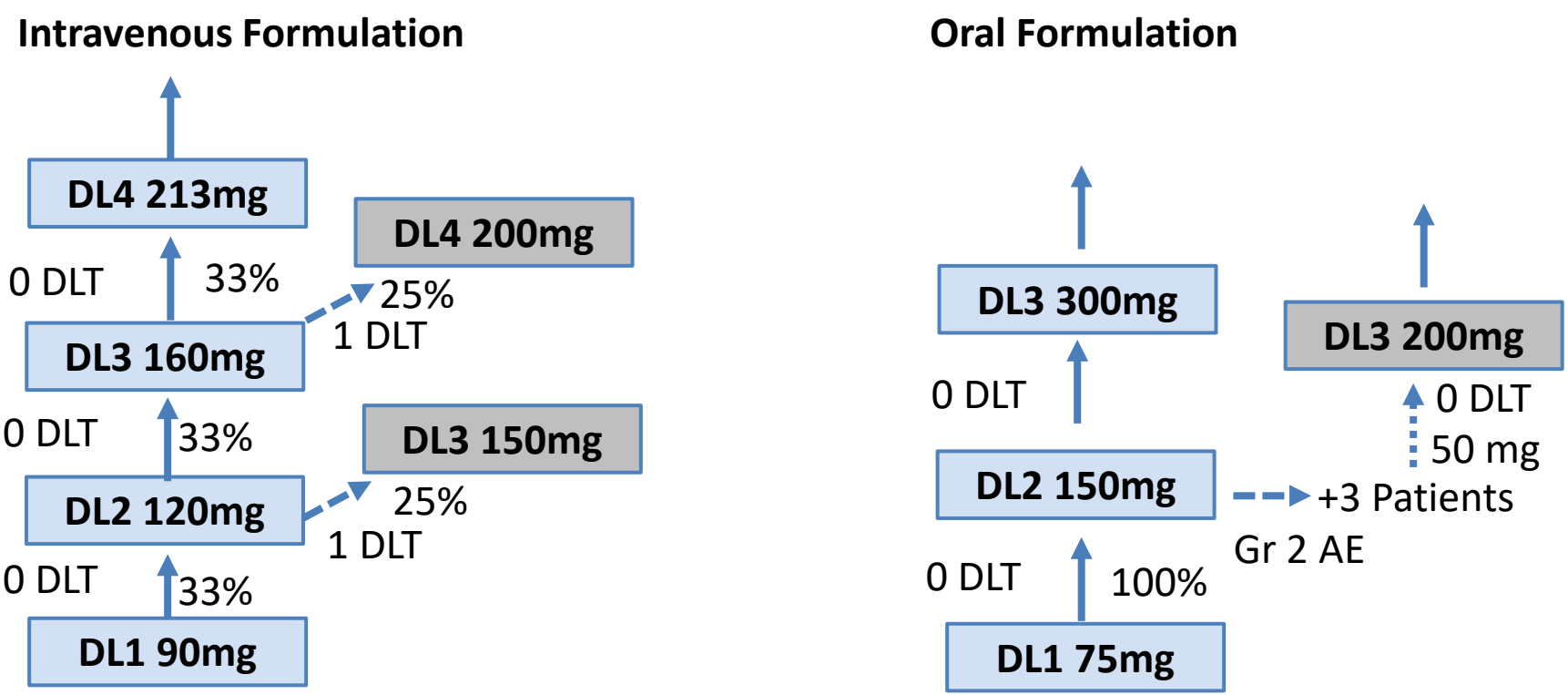
Secondary Objectives:

- To evaluate pharmacokinetics
- To assess pharmacodynamic markers (RNA Pol II CTD P-Ser2 and MCL1 levels in PBMCs)

Design:

- Open label, dose escalation study in patients with advanced solid tumors
- Administration schedule of flat fixed dosing schedule of fadraciclib (CYC065) given either by 1-hour infusion or orally on day 1, 2, 8 and 9 every 3 weeks

Dose Escalation



Key Eligibility Criteria and Dose Limiting Toxicity Criteria

Key Inclusion Criteria:

Advanced solid tumors progressed on standard therapies or have no known effective therapy

ECOG PS 0 – 1

Evaluable disease

Adequate organ function:

- Absolute neutrophil count $\geq$ 1.5 x 10^9/L, platelets $\geq$ 100 x 10^9/L
- Total bilirubin $\leq$ 1.5 x ULN, ALT $\leq$ 1.5 x ULN
- Creatinine $\leq$ 1.5 x ULN or creatinine clearance > 60 mL/minute (Cockcroft formula)

Key Exclusion Criteria:

Untreated CNS metastases or evidence of CNS progression on MRI within 4 weeks prior to enrollment for treated CNS metastases

Dose Limiting Toxicity:

- Grade 3 or 4 non-hematological toxicity (except alopecia, inadequately treated nausea, vomiting and diarrhea)
- Grade 3 or 4 AST/ALT with Grade 2 elevation of bilirubin
- Neutropenic fever or grade 4 neutropenia > 5 days
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding
- Grade 4 anemia
- Treatment delay > 2 weeks due to drug-related adverse events

Maximum Tolerated Dose (MTD): the highest dose level at which less than 2/6 patients experience DLT in cycle 1

Recommended phase 2 dose (RP2D): the dose level at which < 33% of at least 6 patients experienced a DLT in cycle 1

Patient and Disease Characteristics

	I.V. 1-hour infusion (n=24)	Oral (n=5)
Age, median (range)	67 (33 – 84)	57 (52 - 63)
Gender		
Male	4	2
Female	20	3
ECOG		
0	5	-
1	19	5
Type of tumor		
Ovary (serous, clear cell, poorly differentiated)	8	1
Uterine (carcinosarcoma, endometrial, leiomyosarcoma)	3	-
Breast	2	1
Lung	2	-
Rectal	2	-
Other (anal, fallopian, esophageal, parotid, adenoid cystic carcinoma, prostate, urothelial, skin, unknown primary)	7	3

Common Adverse Events

(All cycles, maximum grade, regardless of causalities)

	I.V. 1 hour infusion (n=24)		Oral (n=5)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Anemia	4	1	2	-
Leukopenia	2	2	-	-
Neutropenia	3	1	-	-
Abdominal distension	4	-	-	-
Constipation	8	-	1	-
Diarrhea	14	1	1	-
Nausea	11	-	2	-
Vomiting	10	-	-	-
Fatigue	5	1	-	-
Hyperglycemia	6	2	1	-
Hypoalbuminemia	5	-	-	-
Hypophosphatemia	6	-	1	-
Arthralgia	4	-	-	-
Dyspnea	4	1	-	1

Dose-Limiting Toxicities

I.V. 1-hour infusion (free base equivalent)	Number of patients treated	DLT
90 mg (65.4 mg)	3	-
120 mg (87.2 mg)	5	-
160 mg (116.3 mg)	5	-
213 mg (154.8 mg)	11	Grade 2 Neutropenia >2 weeks (n=1)*
Oral		
75 mg free base equivalent **150 mg** free base equivalent	1 4	- -

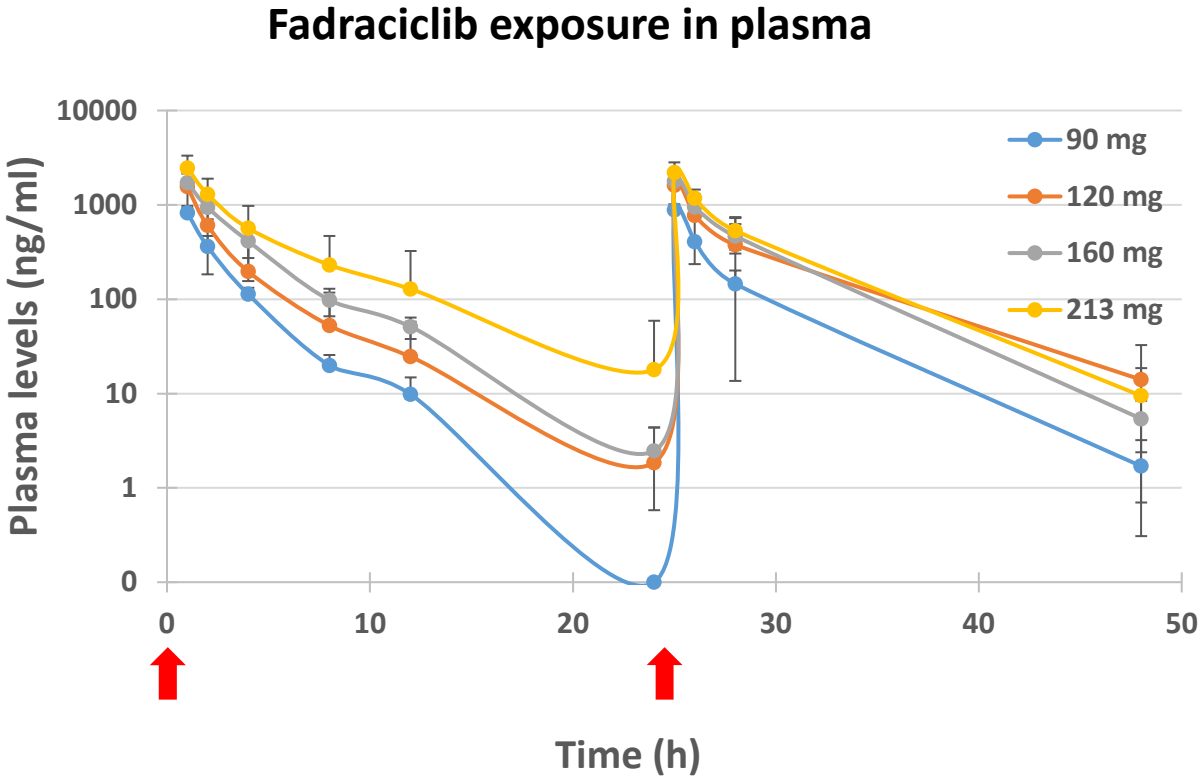
*2 additional patients required dose reduction for transient elevations in AST (gr. 3) and serum creatinine (gr. 2)

Pharmacokinetic Analysis 1h-infusion Day 1 and 2

PK parameters – NCA, WinNonlin 7.0™

Cohort (n)	Day 1					Day 2				
	Half-life	C_{max}	$AUC_{(0-t)}$	Vz	CL	Half-life	C_{max}	$AUC_{(0-t)}$	Vz	CL
(mg)	(h)	(ng/ml)	(h*ng/ml)	(L)	(L/h)	(h)	(ng/ml)	(h*ng/ml)	(L)	(L/h)
90 (3)	1.39	822	1770	87	37	2.7	881	2630	81	21
120 (5)	2.8	1560	3430	106	34	3.31	1610	6670	74	18
160 (3)	2.99	1720	5010	100	23	3.04	1780	8490	61	14
213 (8)	3.51	2460	8190	115	25	3.07	2190	8320	80	18

Pharmacokinetic Analysis 1h-infusion Day 1 and 2



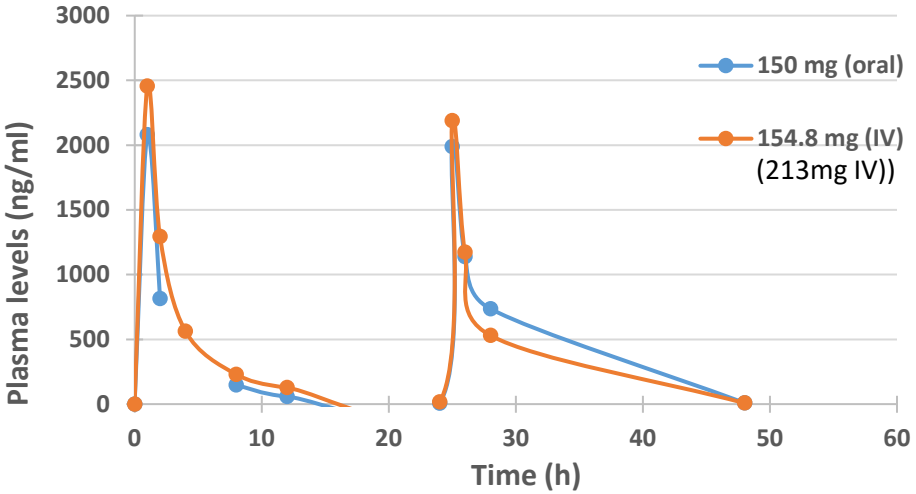
- Exposure increases with dose
- Half-life: 1.4– 3.5 h
- C_{max} up to 6.2 µM; AUC_{inf} up to 20 h*µM
- No accumulation on Day 2
- 50 mg/kg mouse (oral): Avg C_{max} ~5.5 µM; AUC_{inf} ~8 h*µM

Fadraciclib has 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 (213mg IV)	3.51	2460	8190

Fadraciclib plasma levels after oral and 1h-IV infusion

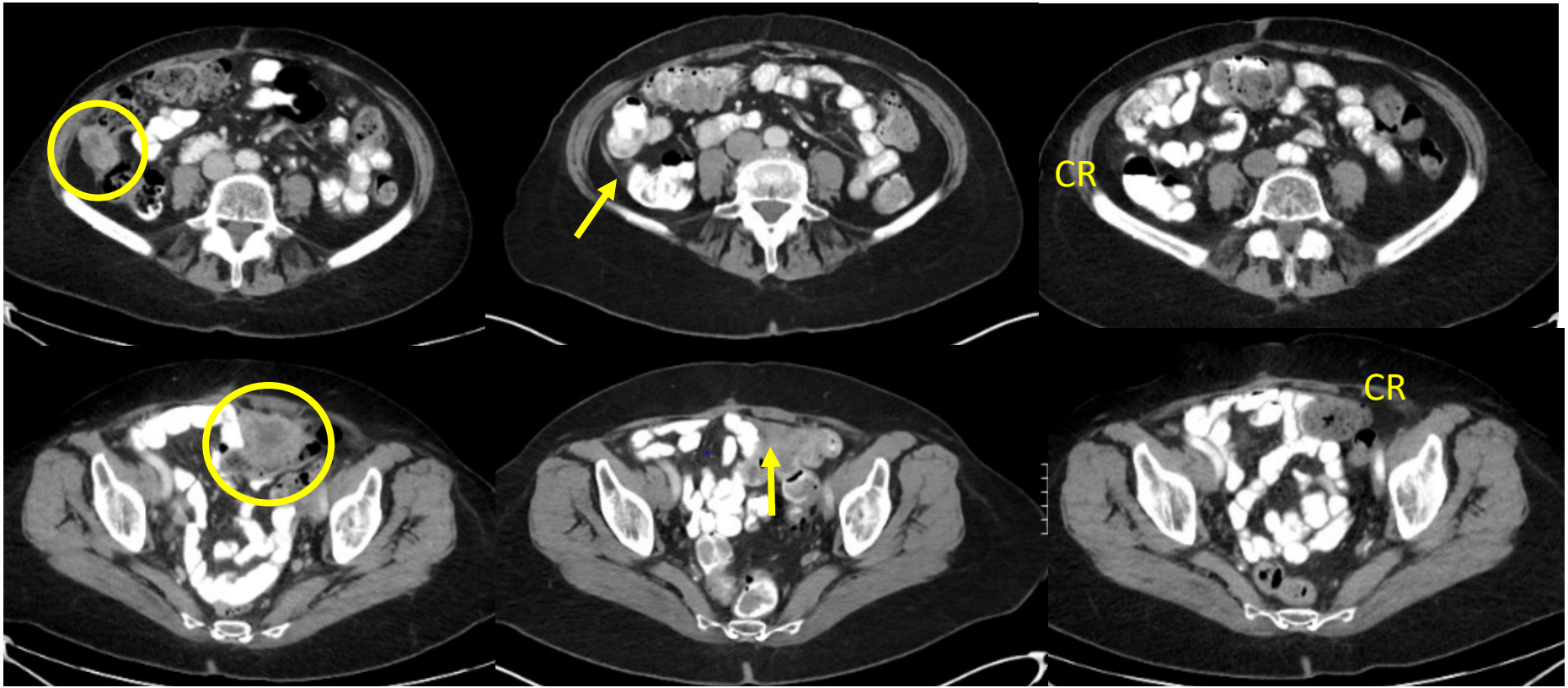


Fadraciclib has comparable PK profiles after oral or 1h-infusion administration

Best Response on Each Dose Level by I.V. 1-h infusion

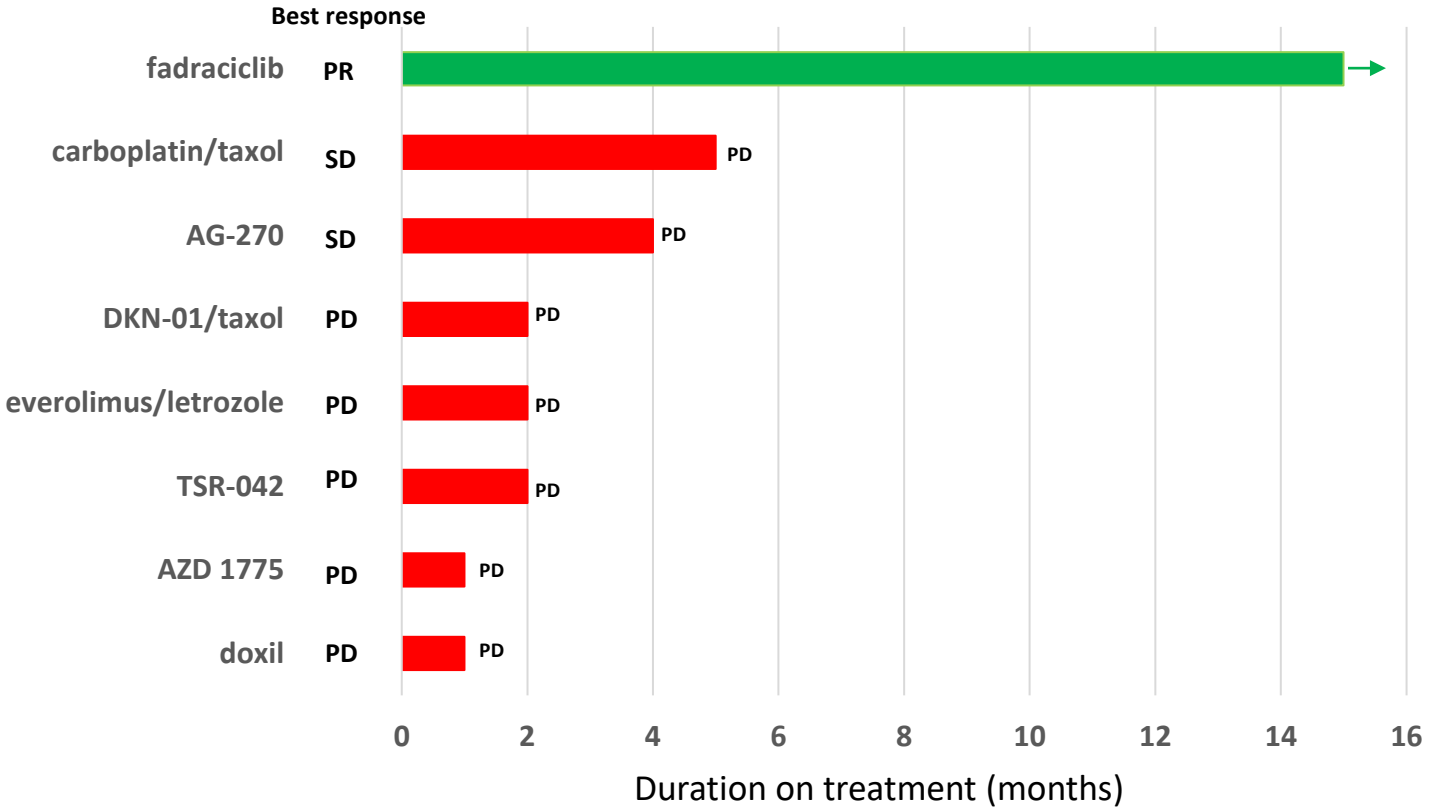
- 90 mg (n=3)
  - 1 SD x 4 cycles (non-small cell lung cancer)
- 120 mg (n=5): No responders
- 160 mg (n=5)
  - 1 SD x 9 cycles (adenoid cystic carcinoma)
- 213 mg (n=11):
  - 1 PR ongoing at 21 cycles (endometrial adenocarcinoma with MCL1 amplification)
  - 1 SD x 5 cycles with 29% target lesion shrinkage (ovarian cancer with cyclin E amplification)
  - 1 SD x 4 cycles (fallopian tube adenocarcinoma)

Clinical response in Mcl-1 amplified endometrial patient



Fadraciclib is most efficacious treatment tested for patient 38

(endometrial adenocarcinoma with MCL1 amplification)



Summary

- Fadraciclib 1-hour infusion, day 1, 2, 8, 9 every 3 weeks is well tolerated and active
  - 1 PR ongoing at 20 cycles in a patient with refractory endometrial adenocarcinoma with MCL1 amplification
  - Stable disease with target lesion shrinkage (29%) in a patient with refractory ovarian cancer with cyclin E amplification

- Pharmacodynamic analyses in PBMCs are ongoing (RNA Pol II CTD P-Ser2 and MCL1 levels)
- 1-hour infusion achieves C_{max} up to 6.2 µM; AUC_{inf} up to 20 h*µM

- Fadraciclib high oral bioavailability, comparable PK as 1-hour infusion
  - More frequent dosing schedules are currently planned

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