FADRACICLIB, AN ORAL CDK2/9 INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMORS AND LYMPHOMA WITH CDKN2A AND/OR CDKN2B GENETIC ALTERATIONS

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BACKGROUND

Fadraciclib: highly selective CDK2 (IC_{50}=5 nM) and CDK9 (IC_{50}=26 nM) inhibitor causing anaphase mitotic catastrophe and apoptotic death of cancer cells at sub-micromolar concentrations. Retrospective review of the dose escalation portion of phase 1 studies suggested clinical activity in patients with known CDNK2A or CDKN2B genetic alterations.

In a Phase 1 study of intravenous fadraciclib monotherapy a heavily pretreated endometrial cancer patient with CDNK2A, CDKN2B and PRMT5 loss achieved confirmed CR.[#]

In the Phase 1 oral fadraciclib monotherapy study (065-101), 7/38 treated patients were found to have known CDKN2A/B genetic alterations, of which 6 were evaluable for efficacy.[@]

- A PTCL patient with CDKN2A P114L mutation reported a PR
- A squamous cell NSCLC patient with CDKN2B loss reported SD and 22% reduction in tumor volume in the sum of all target lesions
- A metastatic, testicular Leydig germ cell cancer patient with CDKN2A, CDKN2B and MTAP loss reported 12% reduction in tumor volume in the sum of all target lesions

Two phase 2 expansion cohorts in the 065-101 study were initiated to evaluate these observations:

- Between April and September 2024, 12 patients with known CDKNA/B genetic alterations were prospectively enrolled in cohort 8.
- Two patients with T-cell Lymphoma were enrolled in cohort 6 which is ongoing.
- All patients were treated with fadraciclib 100mg BID, M-F, week 1-4 in 28-day cycles (RP2D).

METHOD

Patients with known CDK2NA/B genetic alteration (N=12) enrolled in an on-going, open-label, multicenter phase 1/2 study in adult subjects with advanced solid tumors and lymphoma (NCT04983810; CYC065-101) will be presented.

- Phase 1 will explore both schedule and dose of oral fadraciclib monotherapy in 28-day cycles to identify maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D).
- Phase 2 will enroll 12 to 40 subjects in seven specific tumor-type groups and a basket cohort, utilizing a Simon two-stage optimal design to evaluate clinical activity
- Safety, pharmacokinetics (PK) and efficacy will be investigated for all subjects

Primary objectives:

- Dose Escalation: determine MTD and/or RP2D
- Proof of Concept: evaluate preliminary efficacy of fadraciclib as measured by overall response rate (ORR)

Secondary objectives:

- Dose Escalation: assess safety and tolerability, PK, and ORR
- Proof of Concept: assess safety and tolerability; to evaluate disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS)
- Exploratory objectives: investigate clinical pharmacodynamics (PD) and pharmacogenomics (PGx)

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 (B-cell; T-cell)

Cohort 7: mCRC (including KRAS mutated)

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

BASELINE CHARACTERISTICS

	Dose Escalation	Dose Expansion	All patients
N	7	14	21
Age (median, range)	72 (51-81)	63 (34-80)	66 (34-81)
Sex	4M:3F	8M:6F	12M:9F
ECOG PS 0	0	2	2
PS 1	4	12	16
Number of Prior Therapies, median	3	3	3
Cohort 8			
Pancreatic	1	4	5
Cholangiocarcinoma	1	1	2
Melanoma	1	1	2
Cervical ADK		1	1
Ovarian		1	1
Uterine leiomyosarcoma	1		1
Testicular Leydig cell	1		1
Squamous cell unknown primary		1	1
Thymus		1	1
NSCLC squamous cell	1		1
Laryngeal squamous cell		1	1
Duodenal ADK		1	1
Cohort 6			
T-Cell Lymphomas	1	2	3

CONCLUSIONS

Phase 1 studies of fadraciclib suggested clinical activity in patients with known CDNK2A or CDKN2B genetic alterations.

Two expansion cohorts 6 and 8 are evaluating this hypothesis at 100mg BID, M-F, weeks 1-4 in 28-day cycles at which PK was expected to provide optimized drug exposure and tolerability.

Fadraciclib was well tolerated in cohort 8. Most common drug related adverse events included diarrhea, nausea, vomiting and were similar to those seen at this dose in phase 1.

Although fadraciclib demonstrated single agent activity in certain patients, interim efficacy data in ongoing cohort 8 do not currently meet the threshold for further evaluation as monotherapy.

Future studies with fadraciclib are warranted to investigate:

- additional markers of sensitivity to fadraciclib, and
- combinations with current or emerging standard of care in solid tumors of interest and T-Cell lymphoma.

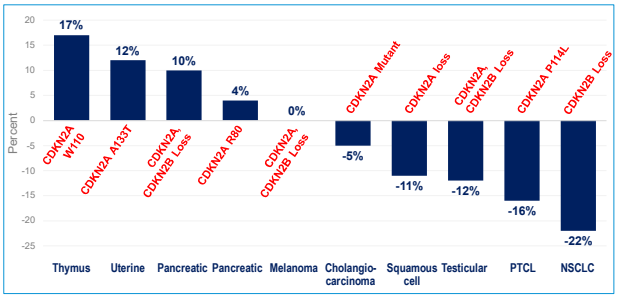
COHORT 8 RELATED TREATMENT-EMERGENT ADVERSE EVENTS (N=12)

System Organ Class (SOC) Preferred Term (PT)	Any Grade n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)
Patients with at least 1 related TEAE	**7 (58.3)**	**3 (25.0)**	**4 (33.3)**	**0**
Gastrointestinal disorders	5 (41.7)	3 (25.0)	2 (16.7)	0
Diarrhoea	2 (16.7)	0	2 (16.7)	0
Nausea	2 (16.7)	2 (16.7)	0	0
Vomiting	2 (16.7)	2 (16.7)	0	0
Investigations	2 (16.7)	1 (8.3)	1 (8.3)	0
Blood creatinine increased	1 (8.3)	0	1 (8.3)	0
Platelet count decreased	1 (8.3)	1 (8.3)	0	0
Metabolism and nutrition disorders	2 (16.7)	1 (8.3)	1 (8.3)	0
Hypocalcaemia	2 (16.7)	1 (8.3)	1 (8.3)	0
Hyperglycaemia	1 (8.3)	0	1 (8.3)	0
Hypokalaemia	1 (8.3)	0	1 (8.3)	0
General disorders & administration site conditions	1 (8.3)	0	1 (8.3)	0
Asthenia	1 (8.3)	0	1 (8.3)	0
Nervous system disorders	1 (8.3)	1 (8.3)	0	0
Dysgeusia	1 (8.3)	1 (8.3)	0	0
Psychiatric disorders	1 (8.3)	1 (8.3)	0	0
Insomnia	1 (8.3)	1 (8.3)	0	0
Renal and urinary disorders	1 (8.3)	1 (8.3)	0	0
Renal failure	1 (8.3)	1 (8.3)	0	0
Vascular disorders	1 (8.3)	1 (8.3)	0	0
Hypotension	1 (8.3)	1 (8.3)	0	0

EFFICACY *(evaluable patients)*

	N	PR	SD	PD	ORR	DCR
Dose Escalation	**6**	**1**	**5**	**-**	**17%**	**100%**
Expansion *(interim data, ongoing)*	*6*	*-*	*2*	*4*	*0%*	*33%*
Total *(interim data, ongoing)*	**12**	**1**	**7**	**4**	**8%**	**67%**

Best % Change from Baseline in Target Lesions (All Response Types)



MOLECULAR CHARACTERISTICS

	CDKN2A	CDKN2B	Best response	Days on treatment	KRAS	TP53	Other alteration
Uterine leiomyo-sarcoma *(50mg BID, MWF, wk 1-3)*	A133T		SD	40			CCNE1, MCL1, MYC
Cholangio-carcinoma *(100mg BID, M-F, wk 1-3)*	CDKN2A mutation		SD	72			FBXW7
PTCL *(100mg BID, M-F, wk 1-4)*	P114L		PR	83			P114L
NSCLC squamous cell *(125mg BID, M-F, wk 1-4)*		Loss	SD	74			
Pancreatic *(125mg BID, M-F, wk 1-4)*	Loss		SD	21			
Melanoma *(150mg QD, wk 1-4)*	Loss	Loss	NE	4			
Testicular Leydig cell *(150mg QD, wk 1-4)*	Loss	Loss	SD	85			MTAP loss
Melanoma	**Loss**	**Loss**	**SD**	**125**		P278F	B2M,CHD2,KDM5C, LATS2, NOTCH2, PTPN11, TERT, TP63, Loss: B2M 1, CHD2, IGF1R 1
Pancreatic	T18fs*15		NE	19	G12D	G245S	BAP1_P555S, SHLD1_K123N
Pancreatic	R58		NE	9	G12D	R175H	MAP2K4_K357E
Pancreatic	Loss	Loss	PD	26	G12D	P250L	MTAP loss, RNF43, ALK, ERBB4
Squamous cell CUP	**Arg80***		**SD**	**85+**		A158H	
Cholangio-carcinoma intrahepatic	Loss	Loss	PD	43		V216M	IDH1, Loss: WT1, MTAP, Gain: HSD3B1, NOTCH2, Ampl. FGFR3, FGFR3-TACC3 Fusion
Thymus	W110		PD	55			SMARCA4
Duodenal ADK	Loss	Loss	NE	7	G12V	R248Q	Gain: BRIP1_ 5, CEBPA_3, Loss: SMAD4, KMT2D, MYH9, NOTCH1, NOTCH2,PDGFR
Pancreatic	R80		PD	24	G12V	V143dup	CCND1, FGF19, FGF3 Ampl., MET_V378I
Ovarian	**Loss**	**Loss**	**TE**	**43+**	G12D		ERCC3, MAP2K1, CHEK2, KMT2C, TMB, Loss regions: TNFRSF14, ERRFI1, PIK3CD, EXOSC10, MTOR, MAD2L2 1
Cervical ADK	L78Fs, V28_ E33del		TE	30		G266R, H214R, R248W	PIK3CA, RAF1 Ampl., ERBB3
Laryngeal squamous cell	**Loss**	**Loss**	**TE**	**21+**		000546.5 :exon4:c. 97-2A>G 64%	ASXL1, ARID1A, AXIN2, BRCA2, DNMT1, FANCD2, FBXW7, MCL1, NFE2L2, PRDM1, SLIT2, TSC1, ZBTB2, Gain: CCND1, FGF19, FGF4, FGF3, Loss: MTAP, RUNX1

Dose Escalation >
< Expansion

[#] Do KT, et al, 32nd EORTC-NCI-AACR Virtual Symposium 24-25 October 2020. [@] Villalona-Calero M, et al, ASCO 2024.
CUP=cancer of unknown primary. PTCL=peripheral T Cell lymphoma. NE=not evaluable. TE=too early for evaluation. Data as of 30 September 2024.

MOLECULAR CHARACTERISTICS

Dose Escalation	CDKN2A	CDKN2B	Best response	Days on treatment	KRAS	TP53	Other alteration
Uterine leiomyosarcoma (50mg BID, MWF, wk 1-3	CDKN2A A133T		SD	40			CCNE1, MCL1, MYC
Cholangiocarcinoma (100mg BID, M-F, wk 1-3)	CDKN2A mutant		SD	72			FBXW7
PTCL (100mg BID, M-F, wk 1-4)	CDKN2A P114L		PR	83			P114L
NSCLC (125mg BID, M-F, wk 1-4)	CDKN2B loss		SD	74			
Pancreatic (125mg BID, M-F, wk 1-4)	CDKN2A loss		SD	21			
Melanoma (150mg QD, wk 1-4)	CDKN2A, CDKN2B loss		NE	4			
Testicular Leydig (150mg QD, wk 1-4)	CDKN2A, CDKN2B loss		SD	85		TP53	MTAP loss
Melanoma	Loss	Loss	SD	125		P278F	B2M:p.A6fs 16%,CHD2:.R804X 63%,KDM5C:E889fs 63%, LATS2:.R1054X 85%, NOTCH2:Y2414X 41%, PTPN11:.Q510H 57%,TERT:G>A 41%, TP63:E609K 43%, Loss: B2M 1, CHD2, IGF1R 1
Pancreatic	T18fs*15		NE	19	G12D	G245S	BAP1_P555S, SHLD1_K123N
Pancreatic	R58*		NE	9	G12D	R175H	MAP2K4_K357E
Pancreatic	Deletion	Deletion	PD	26	G12D	P250L	MTAP_Deletion, RNF43_c, 450+2T>C, ALK_M1615I, ERBB4_S40fs
Squamous cell carcinoma	NM_001195132.1) c.238C>T p.Arg80		SD	85+		A158H	
Intrahepatic Cholangiocarcinoma	Loss	Loss	PD	?		V216M	IDH1:R132C, Loss: WT1, MTAP, Gain: HSD3B1, NOTCH2, Amplification FGFR3 8 copies // MTAP loss // FGFR3-TACC3 Fusion
Thymus	W110*		PD	55			SMARCA4_E882K, SMARCA4_F1507C
Duodenal	Loss	Loss	NE	?	G12V 35%	.R248Q 30%	Gain: BRIP1_ 5, CEBPA_3, Loss: SMAD4, VUS:DIS3:.G279R 14%, KMT2D:.G5468V 15%, MYH9:.E1350D 32%, NOTCH1:.H2125Q 65%, NOTCH2:.I1859T 29%,PDGFRAI1020V 49%
Pancreatic	R80		PD	24	G12V	V143dup	CCND1_Amplification, FGF19_Amplification, FGF3_Amplification, MET_V378I
Ovarian	Loss	Loss	TE	43+	NM_004985.5:exon2:c.35G>A:p.G12D 35%		ERCC3:NM_000122.1:exon3:c.335dup:p.H112fs 45%, MAP2K1:NM_002755.3:exon2:c.145C>T:p.R49C 41%, VUS: CHEK2:NM_007194.4:exon11:c.1180G>A:p.E394K 87%, KMT2C:NM_170606.3:exon42:c.9520G>A:p.D3174N 47%, TMB: 5.22 mutations/megabase, Loss regions: TNFRSF14, ERRFI1, PIK3CD, EXOSC10, MTOR, MAD2L2 1
Cervical ADK	L78Fs, V28_E33del		TE	30+		G266R, H214R, R248W	PIK3CA_E542K, RAF1_Amplification, ERBB3_M91I
Laryngeal squamous	Loss	Loss	NE	21		000546.5:exon4:c.97-2A>G 64%	ASXL1:NM_015338.5:exon11:c.1421_1422dup:p.D475fs 27%, VUS, ARID1A:NM_006015.6:exon18:c.4304A>G:p.Y1435C 24%, AXIN2:NM_004655.4:exon6:c.1583A>G:p.K528R 17%, BRCA2:NM_000059.3:exon20:c.8503T>C:p.S2835P 22%, DNMT1:NM_001379.4:exon5:c.479A>G:p.K160R 28%, FANCD2:NM_001018115.2:exon18:c.1567A>G:p.N523D 23%, FBXW7:NM_033632.3:exon7:c.1041A>G:p.I347M 77%, MCL1:NM_021960.5:exon1:c.112A>T:p.T38S 27%, NFE2L2:NM_006164.5:exon5:c.625G>A:p.E209K 25%, PRDM1:NM_001198.4:exon4:c.481T>A:p.Y161N 41%, SLIT2:NM_001289135.3:exon31:c.3350G>A:p.R1117H 74%, TSC1:NM_000368.4:exon18:c.2302C>T:p.R768C 16%, ZBTB2:NM_020861.3:exon3:c.484C>T:p.Q162X 30%, Gain: CCND1, FGF19, FGF4, FGF3 27 n=27, Loss= MTAP, RUNX1T1