Phase I/II Study of DFP-10917 in Relapsed/Refractory AML Demonstrates Efficacy and Safety Profile Suitable for Phase III Study

#2822

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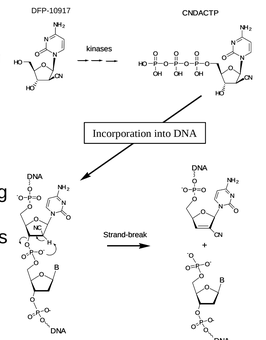
Background

DFP-10917 is a novel deoxycytidine analog, CNDAC (2'-*C*-cyano-2'-deoxy-1-β-D-*arabino*-pentofuranosyl-cytosine), that induces DNA damage in a manner unique from structurally related nucleoside analogs (cytrarabine, decitabine, gemcitabine). Following tri-phosphorylation of 5'-OH in the tumor cell, tri-phosphorylated **DFP-10917** incorporates into replicating DNA when administered at a continuous low dose and self-generates single-strand breaks (SSBs) through β-elimination. These SSBs are further metabolized to double-strand breaks during a subsequent, delayed S-phase when the replication fork encounters the SSB, followed by an arrest in G2 and leading to cell death unless the DSB is repaired through the homologous recombination pathway.



Objectives/Study Design

Primary objective (Phase I):
To determine the MTD, RP2D and DLTs of DFP-10917 administered by 7 or 14 day continuous infusion (CI) in patients with relapsed or refractory acute leukemia.

Phase I	Starting Dose	Regimen
Stage 1	4.0 mg/m^2/day	7-day CI,21-day rest
Stage 2	Calculated as 2/3rd cumulative DFP-10917 dose administered at 7-day MTD divided by 14 days.	14-day CI,14-day rest

Primary objective (Phase II):
To evaluate the overall response rate of DFP-10917, as assessed by CR, CRp, CRi or PR, in patients with relapsed or refractory acute myeloid leukemia.

Phase II Simon 2-stage design	Stage 1	Stage 2
	≥ 1/10	≥ 4/29

Inclusion/ Exclusion/ DLT Criteria

Inclusion criteria:
-Pathologically-confirmed acute leukemia, refractory or relapsed after standard therapy for the disease or for which conventional systemic chemotherapy is not reliably effective or no effective therapy is available. (Phase II permitted on AML diagnosis)
-Aged ≥ 18 years. ECOG Performance Status of 0, 1 or 2.
-Adequate clinical laboratory values (i.e., plasma creatinine ≤1.5 x upper limit of normal (ULN) for the institution, bilirubin ≤1.5 x ULN, alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 x ULN).

Exclusion Criteria:
-Interval from prior treatment to time of study drug administration is < 2 weeks for cytotoxic agents or < 5 half-lives for non-cytotoxic agents. Exceptions: Use of hydroxyurea permitted before the start of study and may be administered up to day 5 of the first cycle.
-Any >grade 1 persistent clinically significant toxicities from prior chemotherapy.
-Extensive prior radiotherapy to more than 30% of bone marrow reserves, or prior bone marrow/stem cell transplantation.

Dose Limiting Toxicity Definition:
-Nausea/vomiting of Grade 3 or greater despite maximal anti-emetic therapy.
-Diarrhea of Grade 3 or greater despite maximal anti-diarrheal therapy.
-Grade 3 or grade 4 AST (SGOT) or ALT (SGPT) elevations that do not return to □grade 2 within 7 days.
-Any other clinically significant Grade 3 or 4 non-hematologic toxicity.
-Pancytopenia in the presence of a hypocellular bone marrow (i.e., cellularity 5% or fewer without evidence of leukemia) that lasts longer than 42 days from the start of therapy.
-Any treatment delay of greater than 2 weeks due to drug-related side effects.

Demographics

Baseline Demographics		Phase 1 Stages 1 and 2 n = 39	Phase 2 Stages 1 and 2 n = 30
Diagnosis	AML	39 (100%)	30 (100%)
	ALL	0	0
Age	Median	69	71
	Range	26-85	45-88
Gender	Male	25	18
	Female	14	12
Racial Group	White	27	25
	Black	4	1
	Asian	1	0
	Other or Unknown	7	4
ECOG	0	7	5
	1	23	22
	2	9	3
Treatment Status	Frontline	1	0
	Salvage 1	9	8
	Salvage 2 ≥	29	22

Phase I Results, DLT and RP2D

DFP-10917 dose (mg/m^2/d)	# of pts enrolled	# of dosing pts	# of evaluated pts	Dose-Limiting Toxicity
Phase I, Stage 1, 7-day dosing: n = 26				
4	3	3	3	None
6	4	4 **	3	None
8	3	3	3	None
10.5	3	3	3	None
14	3	3	3	None
18.5	3	3	3	None
25	3	3	3	None
35	5 *	4	3	1
Phase I, Stage 2, 14-day dosing: n = 12				
10 #	5	5	4	2
6 # #	7	7	6	1
TOTALS	**39**	**38**	**34**	**4**

One patient experienced grade 3 tremors during Cycle 2 infusion of DFP-10917, resulting in treatment discontinuation.

Grade 3 diarrhea during Cycle 1 of study treatment, resulting in treatment discontinuation.

Two DLTs of prolonged hypo-cellularity. DLT pts continued treatment at the 6 or 4 mg/m2/day dose x 14 days CI.

One DLT of prolonged hypo-cellularity.

* Stage 2 starting dose calculated as 2/3rds the cumulative 7-day DFP-10917 dose at the MTD of 30 mg/m^2/day divided by 14-day= 10 mg/m^2/day x 14 days.
# # The MTD/RD was defined as 6 mg/m2/day x 14-day. *One pt refused treatment

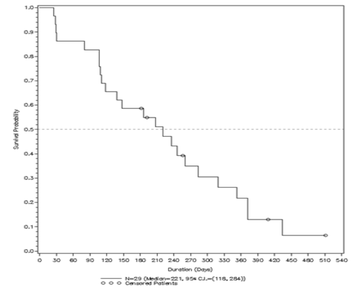
Safety Phase I and II

Drug-Related Toxicity (Reported by 10% or More of Patient)	Phase I (n=38)			Phase II (n=30)		
	Grades 1-2	Grades 3-4	Any Grades	Grades 1-2	Grades 3-4	Any Grades
Gastrointestinal disorders						
Nausea	17 (44.7%)	0	17 (44.7%)	7 (23.3%)	0	7 (23.3%)
Diarrhea	14 (39.5%)	2 (5.3%)	16 (42.1%)	6 (20%)	0	6 (20%)
Constipation	5 (13.2%)	0	5 (13.2%)	7 (23.3%)	0	7 (23.3%)
Stomatitis	5 (13.2%)	0	5 (13.2%)	0	0	0
Vomiting	5 (13.2%)	0	5 (13.2%)	1 (3.3%)	0	1 (3.3%)
Investigations						
WBC count decreased	0	22 (57.9%)	22 (57.9%)	0	15 (50%)	15 (50%)
Blood bilirubin increased	6 (15.8%)	0	6 (15.8%)	0	0	0
Platelet count decreased	0	6 (15.8%)	6 (15.8%)	0	13 (43.3%)	13 (43.3%)
ALT increased	4 (10.5%)	0	4 (10.5%)	0	0	0
AST increased	4 (10.5%)	0	4 (10.5%)	0	0	0
Metabolism/nutrition disorders						
Decreased appetite	5 (13.2%)	0	5 (13.2%)	0	0	0
Fatigue	2 (5.3%)	0	2 (5.3%)	3 (10%)	1 (3.3%)	4 (13.3%)

Reduction in Bone Marrow Blasts

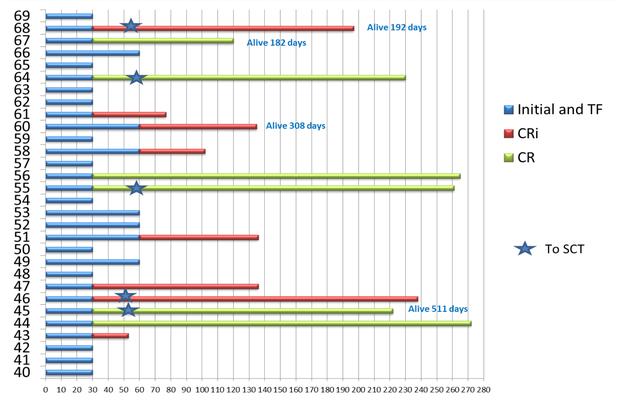
Phase	Patient ID	Dose (mg/m^2)	CI Period	Age (years)	Salvage Status	Prior Rx	Baseline Bone Marrow Blasts	Best Bone Marrow Blasts	< 5% BM Blasts on Day	Response	Treatment Cycle
I	001-01-0006	6	7-day	50	Fifth	Dauno+AraC, MEC, Flu+AraC+Ida, SGI-110	63%	4%	29	CRi	2
	001-01-0029	10 → 6 → 4	14-day	82	Second	Vidaza	82%	0%	22	CR	21
	001-01-0032	10 → 6	14-day	77	Second	SGI-110	48%	3%	146	CRi	5
II	001-01-0043	6	14-day	62	Transformed from CML	Azacitidine, Clof+AraC	34%	2%	22	CRi	1
	001-01-0044	6 → 4	14-day	75	Transformed from MDS	Decitabine, Clof+AraC	56%	1%	58	CR	6
	001-01-0045	6	14-day	79	MDS,Third	Dauno+AraC, Vidaza	35%	2%	21	CR	3 → SCT
	001-01-0046	6	14-day	71	Third	CPX-351, INV-ASP2215	23%	3%	29	CRi	2 → SCT
	001-01-0047	6	14-day	58	Sixth	Ida+AraC,Ida+Flu, Soraf, Mito+Etopo, Cladra+Ida+AraC	22%	0%	22	CRi	4
	001-01-0051	6 → 4	14-day	73	CMML, Third	Aza, Clof+AraC, Rigosertib+Aza	39%	4%	99	CRi	3
	001-01-0055	6	14-day	63	Fourth	Flu+AraC+Ida, SCTx, Decitabine, Clad+AraC+Ida	73%	0%	32	CR	1 → SCT
	001-01-0056	6	14-day	73	Fourth	Ida+AraC, Decitabine, Aza	26%	1%	28	CR	6
	001-01-0058	6	14-day	73	Second	SG-110+Ida	31%	4%	22	CRi	2
	001-01-0060	6	14-day	63	Second	Azacitidine	36%	3%	50	CRi	4
	001-01-0061	6	14-day	71	Third	Decitabine, Dauno+AraC	14%	4%	22	CRi	2
	001-01-0064	6	14-day	61	Third	Dauno+AraC, Mitoxant+AraC+Clad	80%	4%	22	CR	1→SCT
	001-01-0067	6	14-day	71	Second	Vosaroxacin+Decitab	25%	1%	34	CR	3
	001-01-0068	6	14-day	53	Third	Ida+AraC,+Clad, Sorafenib	33%	5%	18	CRi	1—>SCT

Phase II Overall Survival



	Overall Survival
# Patients	N=29
Median	221 days
1 mo (30 days)	86.2%
3 mo (90 days)	82.8%
4 mo (120 days)	65.5%
6 mo (180 days)	58.6%
9 mo (270 days)	34.9%
1 yr (360 days)	21.8%

Phase II Response Duration



Efficacy

Phase I (n=37)

CI Period	DFP-10917 dose (mg/m^2/day)	No. of evaluated patients	Best Response		Response Rate
			CR+CRp+CRi	PR	
7-day	4 - 35	24	1	0	8.3%
14-day	6 - 10	10	2*	0	20.0%

* Two patients continued study treatment at the 6 or 4 mg/m^2/day dose.

Phase II (n=29)

Stage	DFP-10917 dose (mg/m^2/day)	No. of evaluated patients	Best Response				Response Rate
			CR			PR	
			CR	CRp	CRi		
1	6	10	2	0	3	0	50.0%
2	6	19	4	0	5	0	47.3%
Total	6*	29	14				48.3%

* Patients continued study treatment at the 6 or 4 mg/m^2/day dose.

Conclusions

- In Phase I, the MTD/RP2D of DFP-10917 in relapsed AML was established at 6 mg/m^2/day for 14-day CI and 14-day rest.
- Dose limiting toxicities included diarrhea and prolonged hypocellularity.
- One patient received 21 cycles of DFP-10917 CI with continuous CR until relapse.
- In Phase II, DFP-10917 demonstrates significant anti-leukemic activity with a ~50% response rate to DFP-10917 monotherapy and a tolerable safety profile in relapsed or refractory AML.
- The demonstrated therapeutic efficacy of DFP-10917 monotherapy administered by continuous infusion for 14-days of 28 day cycles is a promising AML treatment for multiply relapsed AML patients and further study of DFP-10917 in a randomized phase III study in AML is planned.

COI: KI, CJ and CZ are employees of Delta Fly Pharma, Inc.
No other COIs exist among the authors.