A RANDOMIZED PHASE 2 STUDY OF SAPACITABINE, AN ORAL NUCLEOSIDE ANALOGUE, IN ELDERLY PATIENTS WITH AML PREVIOUSLY UNTREATED OR IN FIRST RELAPSE OR PREVIOUSLY TREATED MDS

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SAPACITABINE

A novel 2'-deoxycytidine nucleoside analogue

Orally available

Converted by amidases to CNDAC *in vivo*

CNDAC is activated by deoxycytidine kinase to CNDAC-triphosphate which:

- Is an efficient substrate for DNA polymerase α for incorporation into DNA
- Introduces single strand DNA breaks via a β-elimination reaction; after several replication cycles, single strand DNA breaks are converted to double strand DNA breaks resulting in cell death
- Induces G2-phase arrest as compared to S-phase arrest by ara-C and gemcitabine
- Causes DNA damage repaired by the homologous recombination pathway

Active against hematologic and solid malignancies in xenograft models

- More active than ara-C in a P388 leukemia model
- More active than gemcitabine in a mammary cancer xenograft model

STUDY RATIONALE

Poor treatment outcomes in older AML patients

- Less likely to achieve CR to standard induction chemotherapy
- No effective and tolerable post-remission therapy
- Increased induction mortality and toxicities from advanced age and pre-existing comorbid conditions

Poor treatment outcomes in MDS patients refractory to hypomethylating agents

New effective drugs are needed to improve disease outcomes

- Sapacitabine has demonstrated promising anti-leukemic activity in relapsed/refractory AML and MDS in a Phase 1 trial

STUDY DESIGN

Open-label, randomized, multi-center, Phase 2 study of 3 dosing schedules

- **Arm A**: 200 mg *b.i.d.* x 7 consecutive days every 3 – 4 wks
- **Arm B**: 300 mg *b.i.d.* x 7 consecutive days every 3 – 4 wks
- **Arm C**: 400 mg *b.i.d.* x 3 consecutive days/wk for 2 wks every 3 - 4 wks

Patient population

- ≥70 years with AML untreated or in first relapse; ≥ 60 years with MDS following hypomethylating agents
- ECOG 0-2
- Creatinine ≤ 1.5 x ULN; total bilirubin ≤ 1.5 x ULN; ALT ≤ 2.5 x or ≤ 5 x ULN if liver involved by leukemia

Primary endpoint: 1-year survival

Secondary endpoints: responses, response durations, hospitalization days, transfusion requirements and safety

Sample size: selection hypothesis

- Total patients: 30 - 60 (10 - 20 per arm) for each stratum
- Bayesian continuous futility monitoring rule for AML stratum
- Early stopping rule for toxicity
- 80% probability to choose the correct dosing schedule if true 1-year survival rate is 45% for better dose arm and 30% for worse dose arm
- May expand dosing schedule with ≥ 4 CR/CRi & ≤ 20% 30-day death rate

Abstract #7021, ASCO Annual Meeting May 29-June 2, 2009 in Orlando, Florida. Supported by Cyclacel Ltd, Dundee, UK. *Poster contains interim data (unaudited) of an ongoing study as of May 2009. CR= complete remission. CRp= complete remission with incomplete platelet recovery. HI= hematological improvement. NA= not applicable or not available. NE= not evaluable. PR= partial remission.*

TABLE 1: ACCRUAL

	Arm A	Arm B	Arm C
Enrolled and treated from 15 US sites	52	29	55
AML			
Original cohort	20	20	20
Expanded cohort	20	-	25
MDS stratum	12	9	10
Patients with ≥ 30 days follow-up			
AML			
Original cohort	20	20	20
Expanded cohort	20	-	24
MDS	11	9	9

TABLE 2: DEMOGRAPHICS

		Arm A	Arm B	Arm C
AML original cohort (n=60)		20	20	20
Age (years):	70 - 80	11	14	14
	> 80	9	6	6
Gender:	Female/male	9/11	7/13	7/13
ECOG:	0 - 1	17	16	18
	2	3	4	2
HCTCI:	0 - 1	10	11	10
	2 or higher	10	9	10
MDS (n=29)		11	9	9
Age (years):	60-69	1	2	3
	70-80	6	4	4
	>80	4	3	2
Gender:	Female/male	3/8	4/5	6/3
ECOG:	0 - 1	8	8	8
	2	3	1	1

TABLE 3: DISEASE CHARACTERISTICS

	Arm A	Arm B	Arm C
AML original cohort (n=60)	20	20	20
Untreated vs. 1st relapse	16 vs. 4	17 vs. 3	15 vs. 5
De novo (1st relapse)	13 (3)	6 (3)	13 (5)
Preceded by AHD (1st relapse) treated:	7 (1)	13	7
▪ with hypomethylating agents	4	8	3
▪ with cytotoxics	-	-	1
Cytogenetics risk by SWOG:			
▪ Intermediate/unknown	14	5	9
▪ Unfavorable	5	11	8
▪ Not available	1	4	3
MDS (n=29)	11	9	9
Prior therapy contains:			
▪ 2 hypomethylating agents	3	3	2
▪ Cytotoxics	-	1	2

TABLE 4: AML RESPONDERS ON 3-DAYS PER WEEK x 2 WEEKS SCHEDULE

Disease	Age (yrs.)	HCTCI	Cyto-genetics	Best Response	Time to Resp. cycles	Total cycles
ARM C: 400 mg *b.i.d.* (n=20) : Overall response rate = 35% including 25% CR, 10% HI						
De novo	72	4	Intermediate	CR	4	>18
De novo	72	1	Unfavorable	CR	6	>12
De novo	82	0	Unfavorable	CR	9	>9
De novo	83	4	Unfavorable	CR	2	5
De novo (1st relapse)	76	2	NA	CR	2	>5
De novo	71	3	Unfavorable	Major HI in platelets & neutrophils; marrow blast 67%↓ to 36%	3	3
De novo	74	0	Unfavorable	Major HI in platelets; marrow blast 40% ↓ to 36%	6	>12

TABLE 5: AML RESPONDERS ON 7-DAY SCHEDULE

Disease	Age (yrs.)	HCTCI	Cyto-genetics	Best Response	Time to Resp. cycles	Total cycles
ARM A: 200 mg *b.i.d* (n=20) : Overall response rate = 45% including 10% CR, 5% PR, 30% HI						
Pre by MDS (1st relapse) *	71	1	Intermediate	CR	1	13
De novo	70	4	Intermediate	CR	1	1
De novo	86	0	Intermediate	PR	2	3
De novo	82	4	Unfavorable	Major HI in platelets; marrow blast 38% ↓ to 5%	7	15
Pre by MDS**	84	3	Intermediate	Major HI in platelets; marrow blast 22% ↓ to 13%	2	> 17
De novo	80	1	Intermediate	Major HI in neutrophils; resolution of leukemic cutis	4	>11
Pre by MDS	81	2	NA	Major HI in platelets; marrow blast 77% ↓ to 5%	2	>9
De novo	79	0	Intermediate	Major HI in neutrophils; marrow blast 90% ↓ to 23%	4	>6
De novo (1st relapse)	77	1	Unfavorable	Major HI in neutrophils; marrow blast 90% ↓ to 2%	1	4
ARM B: 300 mg *b.i.d.* (n=20) : Overall response rate = 25% including 10% CR/CRp, 5% PR, 10% HI						
Pre by MPD	74	0	Unfavorable	CR	3	5
Pre by MDS	82	4	NE	CRp	4	9
De novo (1st relapse)	75	0	Intermediate	PR	3	7
Pre by MDS	80	0	NE	Major HI in platelets	1	1
Pre by MDS**	73	4	NA	Major HI in platelets; marrow blast 43% ↓ to 30%	2	7

**First relapse after decitabine-containing regimen. ** Received hypomethylating agents for preceding MDS. MPD=myeloproliferative disease.*

TABLE 6: MDS RESPONDERS *(on going study stratum)*

Dosing schedule	Age (yrs.)	Prior Treatment	Best Response	Time to Response cycles	Total cycles
Arm A (n=11)	72	azacitidine	CR	3	>6
	64	azacitidine, decitabine	Major HI in neutrophils	2	2
	75	azacitidine, decitabine	Minor HI in platelets	1	>1
Arm B (n=9)	73	azacitidine, decitabine	Major HI in platelets	5	>7
	82	azacitidine, decitabine	Major HI in platelets	2	5
	69	azacitidine, lenalidomide, gemetecan	Major HI in platelets and neutrophils	3	>4
Arm C (n=9)	78	azacitidine, VEGF-TRAP	Major HI in neutrophils	1	>4

TABLE 7: SAFETY

	Arm A	Arm B	Arm C
AML original cohort (n=60)	*20*	*20*	*20*
Days of follow-up (mean)	332	361	272
Number of cycles: median (range)	3 (1 - >17)	3 (1 - 9)	3 (1 - >18)
Patients received ≥ 6 cycles	7	5	5
Number of deaths – all causes	12	15	12
▪ Death within 30 days (possibly drug-related)	2	4 (1)	2
Number of patients with dose reductions	2	7	8
Number of patients still on study	5	-	6
AML expanded cohort (n=44)	*20*	*NA*	*24*
▪ Death within 30 days (possibly drug-related)	3 (2)	NA	3 (1)
MDS (n=29)	*11*	*9*	*9*
Days of follow-up (mean)	147	141	153
Number of cycles: median (range)	1 (1 to >6)	4 (1 to >7)	2 (1 to 9)
Patients received ≥ 4 cycles	3	6	4
Number of deaths – all causes	5	2	2
▪ Death within 30 days (possibly drug-related)	1	-	-

TABLE 8: COMMON ADVERSE EVENTS †

	Arm A			Arm B			Arm C		
Preferred Term	1-2	3-4	5	1-2	3-4	5	1-2	3-4	5
Anemia	5	14	-	1	8	-	11	3	-
Febrile neutropenia	-	9	-	-	11	-	-	11	-
Neutropenia	-	16	-	-	4	-	1	12	-
Thrombocytopenia	-	15	-	-	7	-	1	10	-
Abdominal pain	5	4	-	4	-	-	1	2	-
Constipation	7	-	-	8	1	--	11	-	-
Diarrhea	22	1	-	13	2	-	16	1	-
Nausea	15	1	-	8	-	-	23	1	-
Vomiting	11	-	-	5	-	-	12	-	-
Fatigue	18	2	-	11	1	-	12	1	-
Edema peripheral	7	-	-	9	-	-	9	1	-
Pyrexia	9	1	-	2	-	-	10	-	-
Bacteremia	1	6	-	-	-	-	-	4	-
Pneumonia	-	5	-	1	4	1	2	5	-
Sepsis	-	3	4*	-	-	2	-	2	-
Anorexia	7	1	-	5	-	-	6	-	-
Hypokalemia	7	1	-	2	1	-	4	2	-
Hyponatremia	5	1	-	2	-	-	-	1	-
Back pain	3	2	-	3	-	-	4	-	-
Dizziness	6	-	-	4	-	-	8	-	-
Headache	5	1	-	-	-	-	3	1	-
Cough	7	-	-	3	-	-	4	1	-
Dyspnea	9	2	-	2	-	-	11	2	-
Epistaxis	6	-	-	4	-	-	3	1	-
Alopecia	9	-	-	3	-	-	9	-	-

*† Maximum grade, all cycles, regardless of causality. * Two deaths considered by investigator to be possibly related to drug.*

SUMMARY

Oral sapacitabine is active in AML across all 3 dosing schedules; activity also observed in MDS

Arm C (400mg *b.i.d.* - 3 days/week x 2) in AML has the highest CR rate (25%) with the longest duration

Arm C all-cause 30-day mortality was 9.4%

- **Overall 11.3% among 133 (104 AML, 29 MDS) patients; Arm A: 11.8%; Arm B: 13.8%**

Prolonged administration is feasible in the outpatient setting

- **25 - 35% elderly AML patients received ≥ 6 cycles**
- **27 - 66% MDS patients received ≥ 4 cycles *(study stratum ongoing)***

Further clinical development in AML and MDS is warranted