



# Phase I Study of a Liposomal Carrier (CPX-351) Containing an Optimized, Synergistic, Fixed Molar Ratio of Cytarabine and Daunorubicin in Advanced Leukemias and Myelodysplastic Syndromes

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## Introduction

Drug combinations can have synergistic, additive or antagonistic activity against tumor cells *in vitro* depending on the molar ratio of the individual agents. We used drug delivery technology to overcome the inherently dissimilar PK of individual drugs, thus enabling us to maintain predetermined synergistic ratios after iv administration (Combiplex™ Technology). Applying a Ratiometric Dosing™ approach to combinations of anticancer agents has allowed us to directly translate *in vitro* synergy *in vivo*, resulting in fixed-ratio drug combination formulations with potent therapeutic activity. Our preclinical data has shown that a 5:1 molar ratio of cytarabine: daunorubicin was optimal against 15 cell lines *in vitro* and in 5 murine leukemia models *in vivo*<sup>1</sup>. CPX-351, a liposomal formulation of the combination developed to maintain a 5:1 molar ratio in vivo is being evaluated in a phase I trial (CLTR0305-101).

1. Johnstone S et. al., Proc Amer Assoc Cancer Res 2006; 47:3061

## Methods

Patients with relapsed/refractory AML, ALL and high risk MDS were included. Ninety minute IV infusions of CPX-351 were administered on days 1, 3 and 5 of each induction course. A second induction course was permitted if there was evidence of antileukemic effect and persistent leukemia in a 14 day bone marrow. Dose escalation began at 3 units/m<sup>2</sup> (1 unit = 1 mg cytarabine and 0.44 mg daunorubicin) with single patient cohorts and doubling of doses with each cohort until evidence of antileukemic activity was observed. Thereafter, 3 patient cohorts and 33% dose increments were to be continued until DLTs signaled the end of further dose escalation. Plasma samples for PK were collected on day 1, 3 and 5 of the 1st cycle and analyzed for cytarabine, daunorubicin, and the metabolites ara-U and daunorubicinol by LC-MS/MS. Data presented is as of November 20, 2007.

## Demographics and Disposition

	Cohort									Total
	1-3	4	5	6	7	8	9			
dose (u/m <sup>2</sup> )	3-12	24	32	43	57	76	101			27
	n=4	n=4	n=4	n=4	n=3	n=3	n=5			
<b>Gender</b>										
Male	3	3	4	0	2	3	3			18
Female	1	1	1	4	1		2			9
<b>Age (yr)</b>										
Median	52.5	60.5	64	70	61	60	57			62
Min-Max	25-78	50-76	55-73	44-77	24-66	46-72	49-77			24-78
≥60-75	1	1	3	2	2	2	1			12
≥75	1	1	1	1	1	1	1			4
<b>Race</b>										
Caucasian	3	3	3	4	1	2	4			20
Black	1						1			4
Asian			1	1	2	1	1			4
Other		1								1
<b>ECOG</b>										
0	3			1	1	1	5			11
1		4	2	2	2	2				12
2	1		2	1						4
<b>Type of Leukemia at Diagnosis</b>										
AML	1	4	4	2	3	3	5			22
Secondary AML				1						1
MDS → AML	1									1
ALL	2			1						3
<b>Response to Last Therapy</b>										
None	4	2	3	2	3	1	4			19
CR		2	1	2	2	2	1			8
<b>On Study</b>										
Adverse Event		1		1			2			4
Persistent Leukemia	4	4	4	1	2	4				19
Bone Marrow Transplant							1			1
<b>Current Status</b>										
Alive										
Persistent Leukemia	2		4	1	2	2	3			14
Complete Remission				1						1
Deceased										
2° to leukemia	1	4		2	1		2			10
Study drug related										0
Unknown	1					1				2

## Conflict of Interest Disclosure

CS, LM, AJ and AL are employees of Celator Pharmaceuticals and own stock or stock options in the company. There are no other relevant conflicts of interest to disclose.

## Grade 3, 4 and 5 Non-hematological Adverse Events

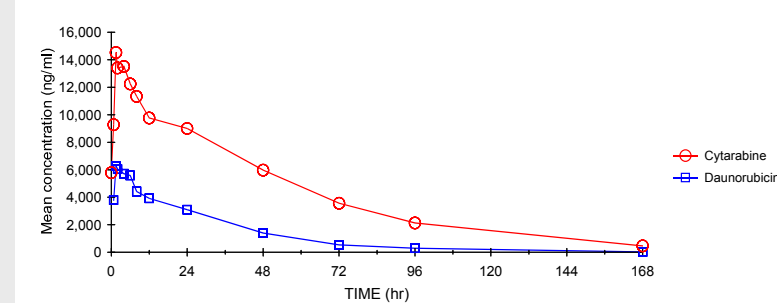
Cohort	1-3			4			5			6			7			8			9			Total			
	3-12			24			32			43			57			76			101						
Dose (u/m <sup>2</sup> )	N=4			N=4			N=4			N=4			N=3			N=3			N=5			N=27			
grade	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5	
<b>Cardiac disorders</b>																									
Cardio-respiratory arrest						1																			1
Troponin increased									1																1
<b>Gastrointestinal disorders</b>																									
Gastrointestinal haemorrhage												1													1
Gingival bleeding																									1
<b>General disorders and administration site conditions</b>																									
Disease progression						1																			1
Pyrexia	1																								
Febrile neutropenia	1					2			1																
<b>Infections and infestations</b>																									
Bacteraemia																									1
C. difficile infection																									1
Infection																									1
Pneumonia																									2
Sinusitis																									1
<b>Metabolism and nutrition disorders</b>																									
Hypokalaemia																									1
Hypophosphataemia																									1
<b>Nervous system disorders</b>																									
Cerebral haemorrhage																									2
Headache																									1
Status epilepticus																									1
<b>Renal and urinary disorders</b>																									
Renal failure acute																									1
<b>Respiratory, thoracic and mediastinal disorders</b>																									
Cough																									1
Dyspnoea																									1
Eosinophilia																									1
Hypoxia																									1
<b>Skin and subcutaneous tissue disorders</b>																									
Rash pruritic																									1
<b>Total Number of Events</b>	<b>2</b>	<b>0</b>	<b>1</b>	<b>6</b>	<b>2</b>	<b>3</b>	<b>3</b>	<b>0</b>	<b>7</b>	<b>0</b>	<b>1</b>	<b>3</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>4</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>4</b>	<b>2</b>	<b>7</b>	<b>4</b>	<b>7</b>

Numbers in red indicate a serious event. Yellow highlighted events were considered related to treatment. \*One pneumonia was related, one was not.

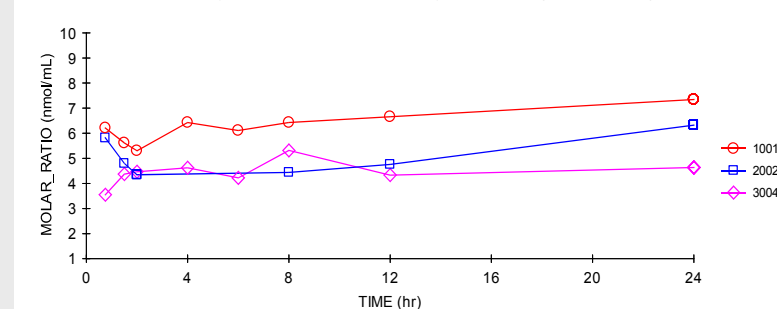
**Drug-related adverse events:** Adverse events considered drug related (possibly, probably) occurred in 19 of 27 subjects. No AE was considered "definitely" drug related. One pt had RSV pneumonia that led to death that was considered possibly drug-related on the basis of drug-related immunosuppression. Single pts had grade 3 GI bleed and rash considered possibly drug related. Seven unique pts had grade 2 drug-related AEs including mucositis (2), diarrhea (1), anorexia (1), pain (2), alopecia (1) and rash (2). The most common drug-related AE was rash, which occurred in 7 unique pts, only one of which had a grade 3 rash.

## CPX-351 Maintains Synergistic 5:1 Molar Ratio in the Plasma

Mean plasma concentration after the day 5 infusion among patients receiving 24 units/m<sup>2</sup> CPX-351 (n=3)



Plasma molar ratio of cytarabine to daunorubicin after the day 5 infusion among patients receiving 24 units/m<sup>2</sup>



Both cytarabine and daunorubicin were detected in the plasma for 168 hours (7 days) after the day 5 infusion.

The molar ratio of cytarabine to daunorubicin was maintained between ~4:1 to 7:1 for 24 hours after the dose.

## CPX-351 demonstrates anti-leukemic activity

Patient	Dose (u/m <sup>2</sup> )	Prior Therapies		Outcome	CPX-351 Inductions	Best Response	Duration (mo)
		Drug	Outcome				
01-001	62yo M AML	24	Cytarabine/daunorubicin/genasense Cytarabine/daunorubicin/genasense Cytosin/Busulfan/HSCT Decitabine	CR-9 mos.	1	↓ in cellularity: 80% to 20%	
04-001	76yo M AML-M5	24	Cytarabine/daunorubicin	CR-4 mos.	1	No Response	
03-004	50yo M AML	24	Mitoxantrone/Etoposide/ Cytarabine HiDAC/Busulfan/cytosin/Methotrexate HCST KW2449	CR-12 mos.	2	No Response	
03-005	59yo F AML	24	Cytarabine/Idarubicin HiDAC	CR- 8 mos.	2	No Response	
02-002	65yo M AML-M5	32	Cytarabine/daunorubicin/cyclosporine HiDAC/cytarabine	CR-4 mos. No Response	2	↓ in cellularity: 20% to 10%	
02-003	63yo M AML-M5	32	Cytarabine/daunorubicin Cytarabine/daunorubicin HiDAC 5-azacytidine Cladribine	No Response CR 4-mons. No Response	2	PR	
03-006	55yo M AML	32	Cytarabine/daunorubicin Cytarabine/daunorubicin HiDAC	CR 2 mos. CR 9 mos. CR 10 mos.	2	CRp	5.3
02-004	73yo M AML-M4	32	Decitabine SNS-595 Triciribine	No Response No Response No Response	1	No Response	
03-007	77yo F AML	43	Zarnestra/etoposide Cytarabine/daunorubicin KW2449	CR- UNK No Response No Response	1	No Response	
03-008	74yo F AML	43	Zarnestra Arsenic/Ara-C Lintuzumab	No Response CR 7-mons. No Response	1	CR	5.6+
01-002	44 yo F ALL	43	Cyclophosphamide/Daunorubicin/ Dexamethasone/vincristine/L-aspar. Gleevec/methotrexate HSCT	CR-8 mos.	1	CR	0.5
02-005	66yo F 2° AML	43	Cytarabine/daunorubicin/etoposide Cladribine/cytarabine	CR- 4 mos.	1	No Response	
01-003	61yo F AML	57	Cytarabine/daunorubicin Cytarabine/daunorubicin (re-induc) HiDAC Idarubicin/ Cytarabine/EL625	No Response CR- 7 mos. No Response	1	No Response	
03-009	24yo F AML	57	Cytarabine/daunorubicin				