

Phase 2 study of CPX-1 liposome injection: UGT1A1 and Prediction of Severe Toxicities



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INTRODUCTION

CPX-1 is a liposomal formulation of irinotecan HCl and floxuridine. The liposomal formulation was designed to deliver a fixed 1:1 molar ratio of the 2 drugs to the tumor, and was based on results from *in vitro* studies which demonstrated broad synergy across multiple solid tumor cell lines for this ratio. CPX-1 had enhanced *in vivo* activity in preclinical models when compared to unencapsulated irinotecan and floxuridine administered at the MTD at various molar ratios and produced promising efficacy in a Phase 1 study. (Proc ASCO 2006 Abst 1414). The Phase 1 study administered CPX-1 by 90 minute infusions every 2 weeks and found the MTD to be 210 units/m². A Phase 2 study was performed to evaluate the efficacy and safety of CPX-1 for patients (pts) with irinotecan-naïve and irinotecan-refractory metastatic colorectal cancer. All pts were to be assessed for UGT1A1 and the safety results were analyzed to see if genotyping could assist in predicting the risk of severe adverse events.

METHODS

This study was a multicenter, open-label, trial. Patients received CPX-1 210 u/m² (210 mg/m² irinotecan + 75.6 mg/m² floxuridine) over 90 minutes every 2 weeks. One cycle was defined as 2 treatments over 4 weeks. Pts were restaged every 2 cycles and all pts restaged at least once are included for efficacy analysis. All pts who received at least part of a dose are included for safety analysis.

Adults with histologically confirmed advanced metastatic colorectal cancer, measurable disease (RECIST) and ECOG performance status of 0 or 1 were eligible. Minimum organ function included: ANC > 1.5x 10⁹/L, platelet count > 100 x 10⁹/L, serum creatinine < 1.5x ULN, serum AST and ALT < 3x ULN (5x if caused by liver metastases), and serum bilirubin < 1.25x ULN (< 2x if caused by liver metastases). Irinotecan-naïve pts had prior treatment with ≤ two regimens overall; one adjuvant/neoadjuvant regimen and no more than one regimen for advanced/metastatic disease. Irinotecan-refractory pts had disease progression within 6 months of prior irinotecan-containing treatment and started CPX-1 treatment within 12 months of disease progression following irinotecan.

DEMOGRAPHICS AND DISPOSITION

	Irinotecan- Naïve				Irinotecan- Refractory				Total All (N=59)	
	6/6 (n=12)	6/7 (n=11)	7/7 (n=2)	Total (n=25)	6/6 (n=12)	6/7 (n=17)	7/7 (n=3)	Total (n=33)		
Gender										
Male	n (%)	5 (41.7)	6 (54.5)	2 (100.0)	13 (50.0)	7 (58.3)	7 (41.2)	3 (100.0)	18 (54.5) ²	31 (52.5)
Female	n (%)	7 (58.3)	5 (45.5)	0 (0.0)	13 (50.0) ¹	5 (41.7)	10 (58.8)	0 (0.0)	15 (45.5)	28 (47.5)
Age (years)	Median	63.5	56	57.5	59	63	59	61	59	59
Race										
White	n (%)	12 (100.0)	7 (63.6)	1 (50.0)	20 (76.9)	11 (91.7)	13 (76.5)	2 (66.7)	27 (81.8) ²	47 (79.7)
Black/African American	n (%)	0 (0.0)	3 (27.3)	0 (0.0)	4 (15.4) ¹	0 (0.0)	2 (12.5)	0 (0.0)	2 (6.3)	6 (10.3)
Asian	n (%)	0 (0.0)	0 (0.0)	1 (50.0)	1 (3.8)	1 (8.3)	1 (6.3)	0 (0.0)	2 (6.3)	3 (5.2)
Other	n (%)	0 (0.0)	1 (9.1)	0 (0.0)	1 (3.8)	0 (0.0)	1 (6.3)	1 (33.3)	2 (6.3)	3 (5.2)
Ethnic Group										
Hispanic or Latino	n (%)	0 (0.0)	1 (9.1)	0 (0.0)	1 (3.8)	0 (0.0)	1 (5.9)	1 (33.3)	2 (6.1)	3 (5.1)
Not Hispanic or Latino	n (%)	12 (100.0)	10 (90.9)	2 (100.0)	25 (96.2) ¹	12 (100.0)	16 (94.1)	2 (66.7)	31 (93.9) ²	56 (94.9)
Weight (kg)	Median	73.6	78.9	63.35	73.4	77.7	72.7	70	73.6	73.6
Height (cm)	Median	163.75	170.2	165.25	165.1	163.6	162	162	162.6	163.7
BSA (m²)	Median	1.85	1.87	1.68	1.84	1.86	1.82	1.79	1.83	1.83
ECOG										
0	n (%)	5 (41.7)	5 (45.5)	0 (0.0)	10 (38.5)	5 (41.7)	11 (64.7)	1 (33.3)	17 (51.5)	27 (45.8)
1	n (%)	7 (58.3)	6 (54.5)	2 (100.0)	16 (61.5) ¹	7 (58.3)	6 (35.3)	2 (66.7)	16 (48.5) ²	32 (54.2)
Patients (%) Ongoing Treatment		0 (0.0)	1 (9.1)	0 (0.0)	1 (3.8)	0 (0.0)	3 (17.6)	0 (0.0)	3 (9.1)	4 (6.8)
Patients (%) Terminating Study		12 (100.0)	10 (90.9)	2 (100.0)	25 (96.2) ¹	12 (100.0)	14 (82.4)	3 (100.0)	30 (90.9) ²	55 (93.2)
Disease Progression		8 (66.6)	6 (54.5)	1 (50.0)	16 (61.5) ¹	6 (50.0)	12 (70.6)	1 (33.3)	19 (57.6)	35 (59.3)
Consent Withdrawn		1 (8.3)	0 (0.0)	0 (0.0)	1 (3.8)	1 (8.3)	0 (0.0)	1 (33.3)	3 (9.1) ²	4 (6.8)
Death		0 (0.0)	1 (9.1)	0 (0.0)	1 (3.8)	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.0)	2 (3.4)
Adverse Event										
Study Drug Related		3 (25.0)	3 (27.2)	1 (50.0)	7 (27.0)	3 (25.0)	2 (11.8)	1 (33.0)	6 (18.1)	13 (22.0)
Not Study Drug Related		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.7)

¹ Includes 1 patient (17-001) that did not have the UGT1A1 assay performed, but was treated.

² Includes 1 patient (02-014) that did not have the UGT1A1 assay performed, but was treated.

Patient characteristics of the irinotecan-naïve and irinotecan-refractory groups were very similar for sex, age, race, ethnicity, weight, height and BSA. The irinotecan-naïve group had a higher proportion of pts with an ECOG Performance Status of 1 (61.5%) whereas the irinotecan-refractory group had a slight majority of pts with an ECOG Performance Status of 0 (51.5%).

ADVERSE EVENTS

	Patients (%)			
	6/6 (n=24)	6/7 (n=28)	7/7 (n=5)	Total All (N=57*)
Deaths on Study	4 (16.6)	3 (10.7)	1 (20.0)	8 (14.0)
Causing Treatment Termination	1 (4.2)	1 (3.6)	0	2 (3.5)
Within 30 days of Study Termination				
Due to Progressive Disease	2 (8.3)	2 (7.1)	1 (20.0)	5 (8.8)
Due to Adverse Events	1 (4.2)	0	0	1 (1.8)
Discontinuations	7 (29.2)	5 (17.9)	2 (40.0)	14 (24.6)
Serious Adverse Events	10 (41.7)	9 (32.1)	4 (80.0)	23 (40.4)
Grade 3 and 4 Adverse Events in 2 or more patients				
Neutropenia/ Febrile Neutropenia	7 (29.2)	6 (21.4)	4 (80.0)	17 (29.8)
Diarrhea/ Nausea/ Vomiting	11 (45.8)	7 (25.0)	2 (40.0)	20 (35.1)
Fatigue	6 (25.0)	1 (3.6)	2 (40.0)	9 (15.8)

* 2 patients that did not have the UGT1A1 assay performed, but were treated are excluded from this table.

Deaths on Study

- 8 pts died on study, including 2 whose deaths lead to treatment termination and 6 who died within 30 days of their last dose of study drug.
- Only one pt died of an adverse event (acute arterial insufficiency) where a contribution by study drug could not be ruled out.
- 5 subjects died of progressive cancer.
- Deaths on study were most frequent in the 7/7 (20%) and 6/6 genotypes (16.6%).

Discontinuations

- 14 patients (24.6%) discontinued treatment as a result of adverse events with no major differences between the irinotecan-naïve (27%) and irinotecan-refractory (18.2%) groups.
- Neutropenia and GI events (diarrhea, nausea, vomiting, and enteritis) led to discontinuations in 7 patients (11.9%)
- Other causes of treatment discontinuation included tumor complications (bowel obstructions, 2 pts), acute arterial insufficiency (1 pt), complication from concomitant medication (1 pt), fatigue and weakness (1 pt), fever and infections (1 pt), major infusion related reaction (1 pt).
- Patients with 7/7 genotype had the highest risk of AE related discontinuations (40%); surprisingly patients with 6/6 genotype had greater frequency of discontinuations (29.2%) than those with 6/7 genotype (17.9%).

Severe Adverse Events

- 23 patients (40.4%) suffered SAEs during this study
 - 80% of the 7/7 genotype patients suffered SAEs.
 - SAE frequency was similar for 6/6 and 6/7 genotype patients (41.7% v 32.1%).

Grade 3 and 4 Adverse Events

- 39 patients (68.4%) suffered grade 3 or 4 AEs including:
 - Neutropenia/ febrile neutropenia: 17 patients (29.8%) with grade 4 events in every genotype.
 - Diarrhea/ nausea/ vomiting: 20 patients (35.1%) with grade 3 events most common in the 6/6 genotype (45.8%) and 7/7 genotype (40%).
 - Fatigue: 9 patients (15.8%) with grade 3 events most common in the 7/7 genotype (40%) and the 6/6 genotype (25.0%).
- 100% of the 7/7 genotype patients had grade 3 or 4 AEs.
- Grade 3 or 4 AEs were more frequent among the 6/6 genotype (79.2%) than the 6/7 genotype (60.7%).

DOSE REDUCTIONS AND DELAYS

	Irinotecan- Naïve				Irinotecan- Refractory				Total All (N=59)
	6/6 (n=12)	6/7 (n=11)	7/7 (n=2)	Total (n=25)	6/6 (n=12)	6/7 (n=17)	7/7 (n=3)	Total (n=33)	
Dose Reduction (# pts)									
210 to 150	8 (66.7)	3 (27.3)	1 (50.0)	12 (46.2)	8 (66.7)	3 (17.6)	2 (66.7)	13 (39.4)	25 (42.4)
150 to 100	3 (25.0)	0 (0.0)	1 (50.0)	4 (15.4)	1 (8.3)	1 (5.9)	0 (0.0)	2 (6.1)	6 (10.2)
210 to 100	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	2 (6.1)	2 (3.4)
Total	8 (66.7)	3 (27.3)	1 (50.0)	12 (46.2)	8 (66.7)	5 (29.4)	2 (66.7)	15 (45.5)	27 (45.8)
Dose Delay Events*									
<7 days	5 (41.7)	4 (36.4)	1 (50.0)	10 (38.5)	2 (16.7)	2 (11.8)	1 (33.3)	6 (18.2)#	16 (27.1)
7 - 13 days	5 (41.7)	4 (36.4)	1 (50.0)	10 (38.5)	5 (41.7)	8 (47.1)	1 (33.3)	14 (42.4)	24 (40.7)
>= 14 days	3 (25.0)	3 (27.3)	1 (50.0)	7 (26.9)	4 (33.3)	8 (47.1)	2 (66.7)	14 (42.4)	21 (35.6)
Total**	8 (66.7)	5 (45.5)	1 (50.0)	14 (53.8)	8 (66.7)	12 (70.6)	2 (66.7)	23 (69.7)#	37 (62.7)
Dose Reduction or Delay	8 (66.7)	3 (27.3)	1 (50.0)	12 (46.2)	8 (66.7)	9 (52.9)	2 (66.7)	19 (57.6)	27 (45.8)

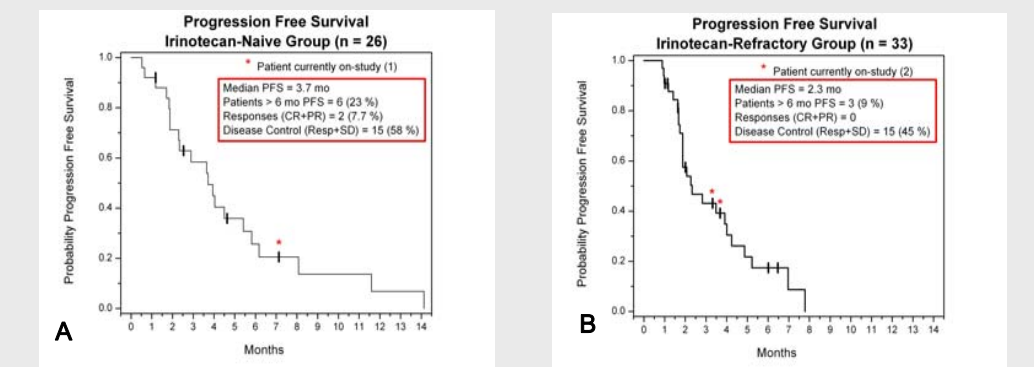
* Each Rx delay event was counted; pts may have had more than one delay event.

** Total counts the # of unique pts with delay events. # includes unknown genotypes

The irinotecan-refractory group had higher rates of dose reductions or delays (57.6% v 46.2%).

UGT1A1 genotyping did not predict dose reductions or delays in that both the 6/6 and 6/7 genotypes had similar rates (66.7% and 60% respectively).

EFFICACY



A) Results for PFS (3.7 mo), RR (7.7%) and disease control (58%) appeared better than results reported by Tournigand, *et al.* for 2nd-line FOLFIRI (4% RR and median PFS of 2.5 mo) and by Sobrero, *et al.* for 2nd-line irinotecan alone (4.2% RR and median PFS of 2.6 mo), in spite of early discontinuation of treatment, dose reductions, and treatment delays. There were 6 pts (23%) with PFS greater than 6 months.

B) The irinotecan-refractory group was similarly affected by dose reductions, treatment delays, and early discontinuations and still achieved a median PFS of 2.3 months, disease control rate of 45%, and had 3 pts (9%) with PFS > 6 months. No objective responses were seen in this group. In spite of the small sample size (n=33) the PFS results appear to be similar to results reported by Van Cutsem *et al.* for panitumumab in the 3rd-line setting (PFS=1.8 months) and cetuximab monotherapy by Cunningham *et al.*

CONCLUSIONS

- The 210 units/m² starting dose produced higher than expected gr 3 and 4 adverse events and treatment discontinuations.
- This resulted in higher than expected dose reductions and treatment delays
- Future studies should start treatment at 150 units/m² with dose adjustments following the first dose.
- UGT1A1 is of limited usefulness in predicting toxicities. Although the 7/7 genotype had the highest risk of gr 3 and 4 toxicities, severe toxicities were more frequent among the 6/6 genotype than the 6/7 genotype and all genotypes had gr 4 adverse events.
- CPX-1 (irinotecan-naïve group) appeared to have better efficacy than irinotecan alone or FOLFIRI in the 2nd line setting and in the 3rd line setting (irinotecan-refractory group) CPX-1 appeared slightly better than panitumumab.

Tournigand C, *et al.* J Clin Oncol 2004; 22: 229-237; Sobrero AF, *et al.* J Clin Oncol 2008; 26: 2311-2319; Van Cutsem E, *et al.* J Clin Oncol 2007; 25: 1658-1664; Cunningham *et al.*, NEJM 2004; 351:337-45