The Mitochondrial Metabolism inhibitor CPI-613 in combination with mFOLFIRINOX for pancreatic cancer

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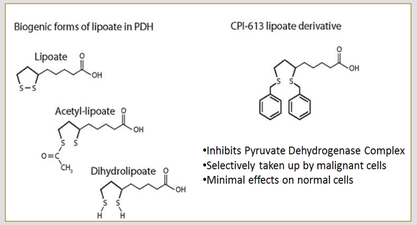
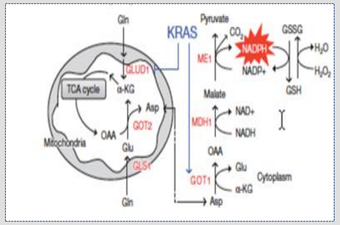
Introduction

Stage IV pancreatic cancer is a lethal disease with limited treatment options. Current standard practice is combination chemotherapy with either FOLFIRINOX or Gemcitabine + Abraxane. Despite these 2 new treatment options, the response rate and survival are limited in stage IV pancreatic cancer. The glycolic and mitochondrial metabolism are aberrant in pancreatic cancer and translate into chemoresistance. Inhibition of glutamine metabolism can potentially synergize with therapies that increase intracellular reactive oxygen species such as chemotherapy. CPI -613 is a novel antimitocondrial developed by Cornerstone Pharmaceuticals.

Figure 1. CPI-613, a Novel Lipoate derivative

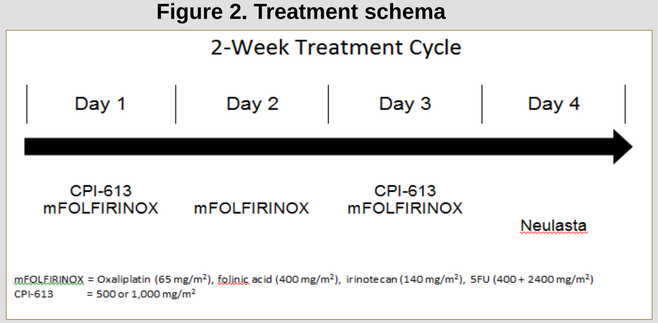




Aims and Methods

- To determine the Maximum Tolerated Dose (MTD) of CPI-613 when used in combination with mFOLFIRINOX, in patients with metastatic pancreatic cancer.
- To assess the safety of CPI-613 + mFOLFIRINOX in patients with metastatic pancreatic cancer
- To obtain preliminary data on efficacy of treatment with CPI-613/ mFOLFIRINOX

Figure 2. Treatment schema



Results

Table 1. Interim Results

Pt #	Treatment			Best Response			
	mFX	CPI=613 (mg/m²)	# of Cycles	RECIST	CA 19-9 (U/mL)		
					Baseline	→	Minimum
001	√	1,000	4	POD	98,000.0	→	33,000.0
002			1	NE	53,000.0	→	NA
003		500	1	NE	1.9	→	NA
004			4	POD	1.1	→	896.0
005			32	PR*	23,000.0	→	3.6
006			16	CR	665.0	→	20.8
007			11	PR	18,000.0	→	2,850.9
008			26	PR*	NL	→	2.9
009			4	SD	43.4	→	33.1
010			8	SD	46,000.0	→	1,067.6
011			4	PR	78.6	→	78.6
012			18	PR	3,221,500.0	→	225.7
013			4	POD	NL	→	NL
014				POD	38,000.0	→	20,000.0
015			10	PR	3,119.1	→	42.5
016			8	PR	3,650.1	→	284.1
017			8	SD	4,527.0	→	1,765.2
018			7	PR	3,749.4	→	1,764.8
019			1		23,042.7	→	NA
020			1		3,223.0	→	NA

*Near CR

Table 2. Adverse Events trial NCT01835041

	Number of Subjects, by CTC Toxicity Grade		
Toxicity	Grade 3	Grade 4	Grade 5
Anemia	3	1	0
Anorexia	1	0	0
Dehydration	3	0	0
Diarrhea	5	0	0
Fatigue	2	0	0
Peripheral sensory neuropathy	1	0	0
Hypokalemia	4	1	0
Hyponatremia	2	0	0
Hypophosphatemia	1	0	0
Hypotension	1	0	0
Hypoxia	1	0	0
Lymphocyte count decreased	5	1	0
Nausea	2	0	0
Neutrophil count decreased	3	0	0
Platelet count decreased	3	1	0
Vomiting	2	0	0
White blood cell decreased	1	0	0

Table 3. Interim Result from trial NCT01835041 vs. Published Phase 3 trial of FOLFIRINOX

	FOLFIRINOX vs. Gemcitabine† *(342 patients 1:1)*	FOLFIRINOX + CPI-613 *(N= 20, 16 evaluable)*
OS (months)	11.1 vs. 6.8	--
CR (n)	1 vs. 0	6% (1)
PR (%)	31 vs. 9.4	50% (8)*
SD (%)	38.6 vs. 41.5	19% (3)
POD (%)	15.2 vs. 34.5	25% (4)
NE (%)	14.6 vs. 14.6	(4)
DOR (months)	5.9 vs. 3.9	
Currently on Rx (n)		8

N Engl J Med 2011;364:1817-25.

Conclusions

CPI-613 is a first in class non-redox active lipoate derivative being tested in phase I clinical trial in combination with mFOLFIRINOX.

The response rate was 56%, which is higher than FOLFIRINOX alone. The treatment combination is feasible and well-tolerated.

The MTD for CPI-613 was identified at 500mg/m^2.

The preliminary efficacy data will inform a randomized phase 2 study of FOLFIRINOX vs. m FOLFIRINOX+ CPI613.

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