Translational Assessment of the Efficacy of CPI-613 Against Pancreatic Cancer in Animal Models Vs. Patients With Stage IV Disease

Avi Retter MD,[1] Claudia Maturo MS,[2] Karen Hoffman MD,[1] John Luddy MS,[2] Robert Rodriguez BSc,[2] Robert Shorr PhD,[2] King Lee PhD [2]

[1] Eastchester Center for Cancer Care, Bronx, NY; [2] Cornerstone Pharmaceuticals, Inc., Cranbury, NJ

Introduction / Background

CPI-613 is a novel agent that selectively targets the altered mitochondrial enzyme function of tumor cells, causing apoptosis, necrosis, and autophagia (1). Results assessing clinical efficacy of CPI-613 translated from animal xenograft models to patients with Stage IV pancreatic cancer are presented.

Methods

Animal Studies: Efficacy of CPI-613 (25 mg/kg), according to tumor growth inhibition and prolongation of survival, was assessed in CD1-Nu/Nu mice with pancreatic tumor xenografts generated by inoculation of BxPC-3 human pancreatic tumor cells. Results were compared to Gemzar® (50 mg/kg, MTD [2]) and non-treated control. Test agents were given intraperitoneally 1x weekly for 4 weeks.

Clinical Studies: The efficacy (assessed according to overall survival) of CPI-613 + Gemzar® was evaluated in patients with Stage IV pancreatic cancer. CPI-613 (70-320 mg/m^2) was given 2x weekly, whereas Gemzar® (1,000 mg/m^2) was given 1x weekly. Both drugs were administered IV on a 3-weeks-on-1-week off treatment cycle.

Results

Animal Studies

Tumor Growth Inhibition: Both CPI-613 and Gemzar® suppressed pancreatic tumor growth when compared to control (Figure 1). Tumor growth inhibition of both agents occurred not only during treatment, but also for at least 4 weeks post treatment. Tumor growth inhibition was greater for CPI-613 than Gemzar®.

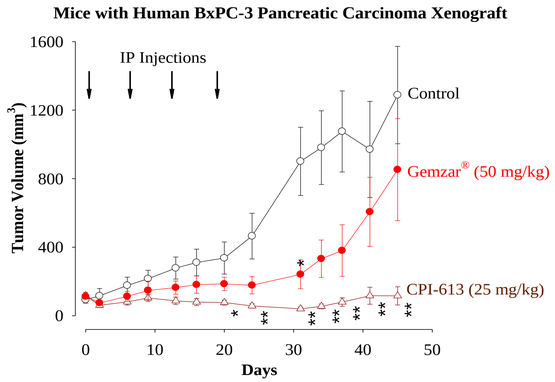

Figure 1: Tumor growth inhibition induced by 4 doses of CPI-613, and to a lesser degree, by Gemzar®, when compared to control treatment in CD1-Nu/Nu mice with pancreatic carcinoma xenografts. n=10/group. * = P<0.05; ** = P<0.01, compared to control.

Results (cont'd.)

Prolongation of Survival: Both CPI-613 and Gemzar® prolonged survival of mice with pancreatic tumor xenografts when compared to control (Figure 2). However, CPI-613 was more effective than Gemzar® in prolonging the survival. The Median Overall Survival for CPI-613 was ~240 days, Gemzar® ~65 days, and control ~50 days.

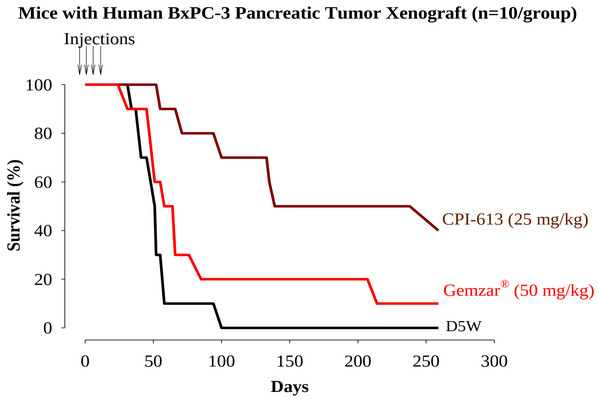

Figure 2: Prolongation of survival induced by 4 doses of CPI-613, and to a lesser degree by Gemzar®, when compared to control treatment.

Clinical Studies

There were 6 patients with Stage IV pancreatic cancer treated with CPI-613+Gemzar® combination (see Table A). The CPI-613+Gemzar® combination was well-tolerated by all 6 patients.

Table A: Patients with Stage IV Pancreatic Cancer Treated with CPI-613+Gemzar® Combination

ID#	Sex	Age	Race/ Ethnicity	Chemotherapy Prior to Study Participation	CPI-613 Dose[a] (mg/m^2)	Survival Since C+G Tx[b] (months)	Survival Since Dx[c] (months)
1-106	M	52	Hispanic	None	70	4.0	4.1
1-110	F	65	Caucasian	None	150	7.4	7.5
1-113	F	77	African American	None	190	>24 (still alive)	>24 (still alive)
1-107	M	63	Caucasian	Gemzar®	105	6.8	9.8
1-111	F	76	African American	5-FU; Gemzar®; FOLFOX+ Transferrin laced Oxaliplatin	150	6	11.3
2-107	M	65	Caucasian	Gemzar®+Tarceva®; Xeloda®+Oxaliplatin	320	2.25	10

[a] CPI-613 was given in combination with Gemzar® (1,000 mg/m^2).
[b] Treatment (Tx) with CPI-613 (C) + Gemzar® (G) (1,000 mg/m^2) combination.
[c] Diagnosis (Dx) of Stage IV pancreatic cancer.

Results (cont'd.)

In the 3 patients who had not received any chemotherapy before participating in the clinical trial, CPI-613+Gemzar® combination prolonged survival that correlated with the dose of CPI-613 (Figure 3).

In the other 3 patients who had received one or more chemotherapies prior to the CPI-613+Gemzar® combination, whether CPI-613+Gemzar® combination prolonged survival could not be determined in this single arm trial.

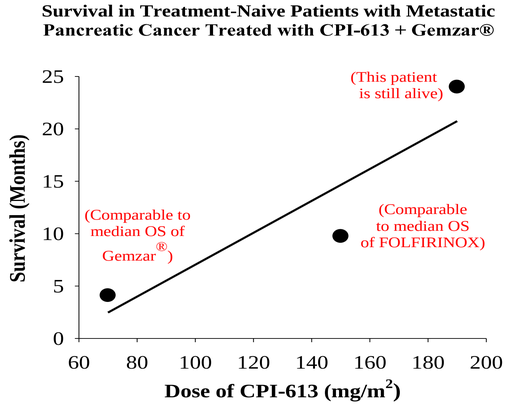

Figure 3: Dose-related prolongation of survival induced by 1000 mg/m^2 of Gemzar® and various doses of CPI-613 in patients with Stage IV pancreatic cancer who had not received any prior chemotherapy.

Summary and Conclusion

1. Only four weekly administrations of CPI-613 provide long-term anti-tumor efficacy in mice with human pancreatic carcinoma xenografts, as reflected by inhibition of tumor growth and prolongation of survival.
2. CPI-613, when used in combination with Gemzar®, also exhibited long-term anti-tumor activities (prolonged survival) in patients with Stage IV pancreatic cancer.
3. Therefore, CPI-613 exhibits efficacy against pancreatic cancer in animal models, which appears translational to patients with Stage IV disease. Further clinical evaluation in this patient population is warranted.

References

1. Zachar Z, Marecek J, et. al. Non-redox-active lipoate derivates disrupt cancer cell mitochondrial metabolism and are potent anti-cancer agents *in vivo*. J Mol Med July 2011 Online. DOI 10.1007/s00109-011-0785-8.
2. Kumer,J. et. al. (Sunesis Poster) 2007. SNS-595 potentiates the *in vivo* anti-tumor activity of carboplatin, cisplatin, and gemcitabine in solid tumor xenografts.