

## **LONG-TERM STABLE DISEASE OF STAGE IV PANCREATIC NEUROENDOCRINE TUMORS AND WITHOUT SIGNIFICANT ADVERSE EFFECT BY CPI-613, AN INVESTIGATIONAL NOVEL ANTI-CANCER AGENT**

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### **ABSTRACT**

The current case study describes the safety and prolonged therapeutic effect of an investigational drug (CPI-613) in a patient (Patient LRW) with Stage IV pancreatic neuroendocrine tumors. Patient LRW was an 88-year old Caucasian woman who was diagnosed with pancreatic neuroendocrine tumors, and had been treated with Sandostatin followed by Enzastaurin. Prior to treatment with CPI-613, she was suffering from progressive Stage IV disease, with lesions located in multiple areas including the pancreas, liver, lung, uterine, stomach, thyroid nodule, etc. During the one-year treatment with CPI-613, only two incidents of mild (Grade 1) and transient adverse events (metallic taste and hyperuricemia) were observed. The Progression-Free Survival was >16 months (Patient LRW still alive as of June 2011), which is consistent with the reported median Progression-Free Survival of 11.4 months with Everolimus treatment and 11.4-12.6 months with Sunitinib treatment. Since the disease remained stable for a year during treatment with CPI-613, Patient LRW was switched to maintenance therapy with CPI-613 and is currently doing well. In Patient LRW, who had Stage IV pancreatic neuroendocrine tumor with Disease Progression, CPI-613 therapy provided long-term Stable Disease and with only 2 minor transient incidents of adverse events during a one-year treatment. This is an uncommon case where chemotherapy with an investigational drug is providing long-term stabilization of advanced metastatic disease without significant adverse events.

**Key words:** Pancreatic neuroendocrine tumors, CPI-613

## INTRODUCTION

Pancreatic neuroendocrine tumors or islet cell tumors display variable malignant potential, hormone-related syndromes (functionality), localization, and genetic background, as in the case with other neuroendocrine tumors. Although patient risk stratification and clinical decisions are related to grading and staging systems, the optimal clinical management of pancreatic neuroendocrine tumors involves a multidisciplinary approach. The epidemiology, pathophysiology, clinical management, and outcomes of patients with neuroendocrine tumors of the pancreas are nicely described by Eneh et al.<sup>1</sup>.

Pancreatic neuroendocrine tumors are rare neoplasms, even when compared with tumors arising from pancreatic exocrine tissue. Researchers differ widely in their estimates of incidence, especially at the level of the secretory/functional subtypes. According to Asian and European population-based studies<sup>2</sup>, the incidence is 1 in 100,000 people, without any gender preference. However, Halfdanarson et al.<sup>3</sup> reported an annual incidence of 2.2 in 1,000,000 people, covering a period of 27 years. There is a male gender preference (males, 2.6; females, 1.8) and a higher incidence in recent decades. Interestingly, the incidence according to autopsy studies is as high as 10%<sup>4</sup>. Furthermore, 19% of all pancreatic lesions incidentally detected by computed tomography (CT) are pancreatic neuroendocrine tumors<sup>5</sup>. These data suggest a higher incidence of clinically “silent” and benign pancreatic neuroendocrine tumors than symptomatic and malignant pancreatic neuroendocrine tumors.

Surgery is the only therapy that can cure pancreatic neuroendocrine tumors. Once metastasis has occurred, most neuroendocrine carcinomas are non-resectable. The most common nonsurgical therapy is chemotherapy, although chemotherapy is largely ineffective for carcinoids, not particularly long-lasting for metastatic pancreatic neuroendocrine tumors, and inappropriate for pancreatic endocrine carcinomas of nonpancreatic origin<sup>6</sup>. When initial chemotherapy fails, the most common therapy is additional chemotherapy with a different set of agents. The benefit from one agent is not highly predictive of the benefit from another agent, except that the long-term benefit of any agent is likely to be low. Possible chemotherapeutic agents include interferon, somatostatin analogs such as Sandostatin® LAR®, growth factor inhibitors such as imatinib, sunitinib, temozolomide, thalidomide, sorafenib, and panitumumab. Other therapies include somatostatin-analog-based radiotherapy, which involves a radioisotope chemically conjugated to a somatostatin analog. Radiofrequency ablation (RFA) and cryoablation are other possible therapies, usually used in patients who have only relatively few metastases. For liver metastatic pancreatic neuroendocrine tumors, there is no established standard therapy<sup>7</sup>. A therapy for liver metastasis is hepatic artery embolization (HAE), which involves injections of embospheres (or microspheres of glass or resin) into the hepatic artery to occlude the blood flow to the tumors<sup>7</sup>. Another therapy is hepatic artery chemoembolization or transarterial chemoembolization, which involves injections of chemotherapy agents into the hepatic artery to provide a higher proportion of the chemotherapy agents delivered to the hepatic lesions<sup>7</sup>. Unfortunately, none of the current therapies have demonstrated any curative or long-term survival benefit. Development of new therapies for pancreatic neuroendocrine tumors is desperately needed.

## CPI-613 and stage IV pancreatic neuroendocrine tumors

Mitochondria of tumor cells are different from that of normal cells due to re-organization of the metabolic machinery causing tumor mitochondria to generate large amounts of biosynthetic precursors to enable tumor cells to thrive in hypo-vascularized, hypoxic microenvironments<sup>8-9</sup>.

The alterations of tumor mitochondria include changes in mitochondrial membrane lipid contents, shifting reliance on glycolysis from oxidative phosphorylation as the primary sources of deriving ATP, and changes in mitochondrial enzymes such as Pyruvate Dehydrogenase (PDC) and  $\alpha$ -ketoglutarate dehydrogenase (KDH), etc.<sup>10</sup>

CPI-613 is a novel anti-cancer agent with mechanism of action that does not belong to any existing pharmacological class of anti-cancer agents currently used in the clinics, and CPI-613 is referred to as an Altered Energy Metabolism-Directed (AEMD) compound. Although structurally similar to lipoate, CPI-613 has activities that are distinctively different from lipoate. Specifically, CPI-613 selectively targets the altered form of mitochondrial energy metabolism found in tumor cells, causing changes in mitochondrial enzyme activities and redox status which lead to apoptosis, necrosis and autophagia of tumor cells, and yet not affecting the mitochondrial energy metabolism of normal cells<sup>8,10,11</sup>. These activities of CPI-613 are due to its involvement in the catalytic and regulatory functions of the tumor or altered form of PDC and KDH found in tumor cells<sup>10</sup>.

Consistent with the proposed novel mechanism is the fact that CPI-613 has been shown to have anti-tumor activity in cell culture and animal tumor models against diverse cancers independent of multiple drug resistance<sup>11</sup>. Clinical, toxicology, drug metabolism, and other results of CPI-613 have been published<sup>11-14</sup>.

The current case study describes the safety and therapeutic effect of an investigational drug (CPI-613) in a patient (Patient LRW) with Stage IV metastatic pancreatic neuroendocrine tumors. There were only 2 transient Grade 1 adverse effects during the one-year treatment with CPI-613, and the disease was stable during for >16 months since the start of CPI-613 therapy. This is one of the few cases where chemotherapy is providing long-term benefits, both in safety and stabilization of disease, associated with pancreatic neuroendocrine tumors.

## CASE REPORT

### A. Background, Disease and Treatment History of the Patient

Patient LRW was an 88-year old Caucasian woman who was diagnosed with Stage IV metastatic pancreatic neuroendocrine carcinoma on 11 July 2006. Patient LRW received Sandostatin chemotherapy starting in October 2006. Sandostatin chemotherapy was stopped in February 2007 due to toxicity. Patient LRW was then placed on Enzastaurin chemotherapy in April 2007, and the Enzastaurin was stopped in June 2009 due to Disease Progression.

At that point, the disease of Patient LRW was at Stage IV, with lesions located in multiple areas within the body including the tail of pancreas and multiple areas of the liver, the lung, uterine, stomach, thyroid nodule, etc. Additional imaging studies in early 2010 showed further Disease Progression, prompting Patient LRW to participate in a clinical trial of an investigational product.

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## B. Participation in Clinical Trial of CPI-613

Patient LRW was enrolled in the clinical trial (Study# CL-CPI-613-002) of the investigational product (CPI-613) at one of the study sites (Premier Research Group Limited, formerly Pivotal Research). Study# CL-CPI-613-002 was a dose-escalation Phase I trial of CPI-613. This study required that patients in this trial initially receive one cycle of treatment of CPI-613 at a specific dose level. Each treatment cycle involved intravenous infusion of CPI-613 over two hours, given twice weekly for three weeks followed by a week of rest (i.e., 3-weeks-on-1-week off). If patients exhibited Stable Disease or better, and without any significant adverse events, additional treatment cycles at the same dose level could be given to the patients. Alternatively, patients could also participate at a different cohort treated with a higher dose level of CPI-613 via the intra-patient dose escalation scheme, provided the patients did not have Disease Progression and met eligibility.

Patient LRW participated in the clinical trial of CPI-613 from 5-April-2010 till the end of March 2011 (approximately one year). While participating in the trial, Patient LRW continuously received treatment with CPI-613. There were a total of 13 treatment cycles at three different dose levels, as shown in Table 1. The conditions of the disease and potential adverse effects of CPI-613 were monitored based on imaging studies (FDG-PET/CT), blood work, urinalysis, ECG, clinical signs, symptoms, etc., performed before and during participation in the trial.

Table 1. Dates related to treatment cycle number and imaging studies of patient LRW, prior to switching to maintenance therapy with CPI-613.

Date of Events			CPI-613 Treatment		FDG-PET/CT
Year	Month	Day	Dose (mg/m <sup>2</sup> )	Start of Cycle#	
2010	April	1			√
		5	588	Cycle 1	
		28			√
	May	3	588	Cycle 2	
	June	1	588	Cycle 3	
		23			√
		28	760	Cycle 1	
	July	22			√
		26	760	Cycle 2	
	August	23	760	Cycle 3	
	September	15			√
		20	1000	Cycle 1	
	October	14			√
		18	1000	Cycle 2	
	November	16	1000	Cycle 3	
December	13	1000	Cycle 4		
	28			√	
2011	January	10	1000	Cycle 5	
	February	2			√
		7	1000	Cycle 6	
	March	7	1000	Cycle 7	
31				√	

## CPI-613 and stage IV pancreatic neuroendocrine tumors

## C. Assessment of Safety and Tolerability of CPI-613 During Participation of Clinical Trial of CPI-613

During the entire year of participation in the clinical trial of CPI-613, the safety and disease of CPI-613 in Patient LRW was assessed based on blood work (including hematology, clinical chemistry, coagulation, etc.), urinalysis, ECG, clinical signs, and symptoms. There were only 2 transient Grade 1 adverse events during the one-year treatment with CPI-613. One incident was metallic taste in the mouth and the other was hyperurcemia (Table 2). Both of these incidents were transient and of Grade 1 level according to National Cancer Institute (NCI) Common Trial Toxicity Criteria (CTC). Therefore, CPI-613 was well tolerated. The minor and transient adverse events associated with CPI-613 were in sharp contrast to treatment with Afinitor® (Everolimus) and Sutent® (Sunitinib), which induced various adverse events in pancreatic neuroendocrine tumor patients ranging from Grade 1 through 4 (see Table 2).

Table 2. Comparative progression free survival and adverse event information of patient LRW Vs. pancreatic neuroendocrine tumor patients in clinical trials of Afinitor® (Everolimus) and Sutent® (Sunitinib)<sup>a</sup>

Clinical Trial (Trial# C2324) of Afinitor® (Everolimus)			Clinical Trial (Trial# A6181111) of Sutent® (Sunitinib)			Clinical Trial (Trial# 002) of CPI-613	
Progression Free Survival, Expressed as Median (95% CI), months <sup>b</sup>							
Everolimus (N=207)	Placebo (N=203)		Sunitinib (N=86)	Placebo (N=85)		CPI-613 (Pt LRW)	
13.7 (11.2-18.8)	5.7 (5.4-8.5)		11.4 (7.4-19.8)	5.5 (3.6-7.4)		>16 <sup>c</sup> (--)	
11.0 (8.4-13.9)	4.6 (3.1-5.4)		12.6 (7.4-16.9)	5.4 (3.5-6.0)			
11.4 (10.8-14.8)	5.4 (4.3-5.6)		10.2 (7.4-16.9)	5.4 (3.4-6.0)			
Incidents of Adverse Events, Expressed as Incidents (% of Incident)							
Grade 1-5 AEs >30%	Everolimus (N=204)	Placebo (N=203)	Grade 1-5 AEs >20%	Sunitinib (N=83)	Placebo (N=82)	Grade 1-5 AEs >0%	CPI-613 (Pt LRW)
Total	203 (99.5%)	198 (97.5%)	Total	82 (98.8%)	78 (95.1%)	Total	1 (100%)
Stomatitis	142 (69.6%)	40 (19.7%)	Diarrhea	49 (59.0%)	32 (39.0%)	Metallic Taste	1 (100%)
Rash	121 (59.3%)	38 (18.7%)	Nausea	37 (44.6%)	24 (29.3%)	Hyperuricemia	1 (100%)
Diarrhea	101 (49.5%)	20 (9.9%)	Asthenia	28 (33.7%)	22 (26.8%)		
Fatigue/Malaise	91 (44.6%)	55 (27.1%)	Vomiting	28 (33.7%)	25 (30.5%)		
Edema	80 (39.2%)	24 (11.8%)	Fatigue	27 (32.5%)	22 (26.8%)		
Abdominal Pain	74 (36.3%)	65 (31.9%)	Hair color changes	24 (28.9%)	1 (1.2%)		
Nausea	65 (31.9%)	66 (32.5%)	Neutropenia	24 (28.9%)	3 (3.7%)		
Pyrexia	63 (30.9%)	26 (12.8%)	Abdominal pain	23 (27.7%)	26 (31.7%)		
Headache/Migraine	62 (30.4%)	30 (14.8%)	Hypertension	22 (26.5%)	4 (4.9%)		
			Hand-foot syndrome	19 (22.9%)	2 (2.4%)		
			Anorexia	18 (21.7%)	17 (20.7%)		
			Stomatitis	18 (21.7%)	2 (2.4%)		
			Dysgeusia	17 (20.5%)	4 (4.9%)		
			Epistaxis	17 (20.5%)	4 (4.9%)		

CI = Confident Interval; N = Total number of patients.

<sup>a</sup> Information obtained from FDA Oncology Drugs Advisory Committee (ODAC) meeting on 12 April 2011.

<sup>b</sup> Different median and the corresponding 95% CI values of Progression Free Survival were derived from analyses by different groups using slightly different criteria.

<sup>c</sup> Patient is alive, as of June 2011.

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## D. Assessment of Disease Conditions During Patient's Participation of Clinical Trial of CPI-613

During the entire year of participation in the clinical trial of CPI-613, the disease of Patient LRW was assessed qualitatively via FDG-PET/CT scans, and via clinical signs and symptoms. There were no signs or symptoms of any Disease Progression. FDG-PET/CT scans indicated that Patient LRW had Stable Disease during the entire year with CPI-613 treatment.

The disease of Patient LRW was further assessed quantitatively according to Response Evaluation Criteria in Solid Tumors (RECIST<sup>15</sup>). These quantitative results are shown in Figure 1. The results indicated that the SUV values of the target lesions (defined according to RECIST<sup>15</sup>) were slightly reduced during the one-year treatment with CPI-613, indicating that there were small reductions in glucose metabolism in these tumor lesions. The longest diameters of the same target lesions were either slightly increased or not changed (although considered Stable Disease according to RECIST<sup>15</sup>) during one-year treatment with CPI-613. The slight increase in the lesion size may be due to CPI-613 inducing necrosis in the tumor lesions, a phenomenon that was observed in animal tumor models.

The non-target lesion (also defined according to RECIST<sup>15</sup>) remained stable during the year when Patient LRW received CPI-613 therapy.

## E. Comparative Information Related to Pancreatic Neuroendocrine Tumor in Current Case Study Vs. Published Information

There were only 2 adverse events during the one-year of treatment with CPI-613. One incident was metallic taste in the mouth and the other was hyperuricemia (Table B). Both were transient and of Grade 1 level according to NCI CTC. The minor and transient incidents of adverse events associated with CPI-613 was in sharp contrast to treatment with Afinitor® (Everolimus) and Sutent® (Sunitinib), which induced various adverse events in pancreatic neuroendocrine tumor patients ranging from Grade 1 through 4 (see Table B). Additionally, Afinitor® (Everolimus) induced adverse related death in 7 out of 204 pancreatic neuroendocrine tumor patients, as compared to only 1 of 203 pancreatic neuroendocrine tumor patients in the placebo group. Sutent® (Sunitinib) induced death in 2 of 83 pancreatic neuroendocrine tumor patients due to cardiac failure, as compared to no cardiac failure related deaths out of 82 pancreatic neuroendocrine tumor patients in the placebo group.

The survival of Patient LRW with CPI-613 treatment is comparable to those treated with the approved product, Afinitor® (Everolimus) and Sutent® (Sunitinib) (Table B). Specifically, for Progression-Free Survival (PFS), it was >16 months (Patient LRW still alive as of June 2011) with CPI-613 treatment for Patient LRW, which is comparable to the median PFS of 11.0-13.7 months with Afinitor® (Everolimus) treatment and 10.2-12.6 months with Sutent® (Sunitinib) treatment.

## F. Maintenance Therapy

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Since the disease has remained stable for a year, and there were only minor and transient adverse events, during treatment with CPI-613 under Clinical Trial CL-CPI-613-002, there was little reason for Patient LRW to continue to participate in the trial.

Accordingly, Patient LRW was switched to maintenance therapy with CPI-613. The maintenance therapy was performed under a Physician-Sponsored Individual Patient Investigational New Drug (IND) application. Patient LRW was doing well when this Case Study was written.

### **DISCUSSION**

The information related to the anti-tumor effects of CPI-613 on Patient LRW was derived from a clinical trial (Study# CL-CPI-613-002). In this clinical trial, the safety and anti-tumor activities of CPI-613 was assessed via a dose-escalation scheme, starting from 21 mg/m<sup>2</sup> to currently 3000 mg/m<sup>2</sup>, with each dose levels having 1-6 patients of various tumor types treated with CPI-613 as monotherapy. There was no comparative drug used in this clinical trial. Patient LRW was the only patient with pancreatic neuroendocrine carcinoma in this trial, while the rest of the patients had other types of colon cancer, pancreatic carcinoma, etc. The anti-tumor activities of CPI-613 in other patients of this trial have been presented in other publications<sup>28-29</sup>. This is the only publication related to this case.

Since this case study involves a single patient with an uncommon cancer (pancreatic neuroendocrine carcinoma), no statistics were actually performed on the results derived from this patient. However, Stable Disease assessed by PET-CT scans performed routinely during the year when Patient LRW received CPI-613 therapy (see Figure 1) was confirmed by contrast (IV and oral contrast) CT performed periodically and independently during the study. As a matter of fact, the size of the lesions derived from the CT portion of PET/CT were identical to that derived from contrast CT. Also, the imaging scan results indicating Stable Disease were consistent with a lack of signs and symptoms of disease progression.

### **CONCLUSION**

In Patient LRW who had advancing Stage IV pancreatic neuroendocrine tumor, CPI-613 therapy provided long-term Stable Disease and with only 2 transient Grade 1 adverse events during the one-year therapy. This is an uncommon case where chemotherapy with an investigational drug is providing long-term stabilization of the advancing Stage IV metastatic stage of this disease, and without troubling adverse events as observed in drugs (Afinitor® [Everolimus] and Sutent® [Sunitinib]) recently approved in the US for the treatment of this disease.

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### Quantitative Assessment of Targeted Lesions of Patient LRW Derived from PET-CT Scans During CPI-613 Treatment

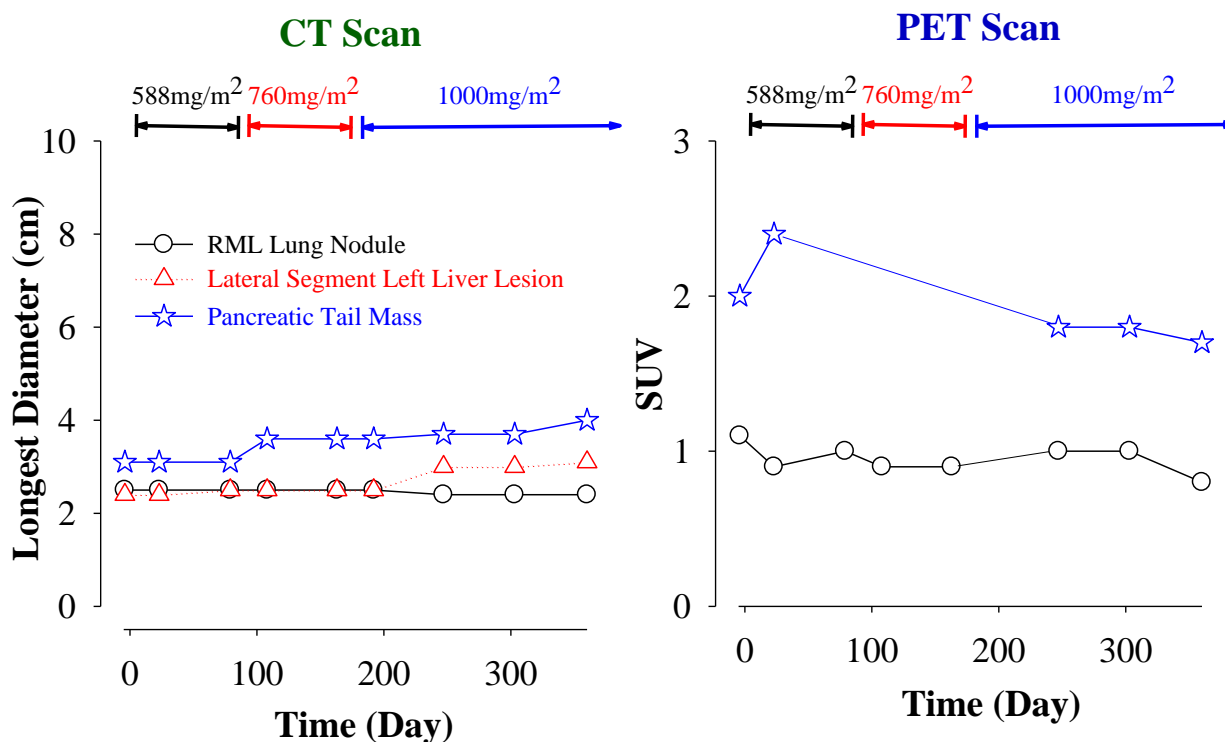


Figure 1: The longest diameter (left) derived from the CT portion of PET/CT scans and the Standardized Uptake Value (SUV) from the PET portion of PET/CT scans of the targeted lesions of Patient LRW during Patient LRW's participation in the clinical trial of CPI-613 (Study# CL-CPI-613-002). The CT portion of the PET/CT scans has been established to be of diagnostic quality and is comparable to contrast (IV and oral contrast) CT. Targeted lesions are defined according to Response Evaluation Criteria in Solid Tumors (RECIST<sup>15</sup>). The results show that the longest diameters of the target lesions were either slightly increased or not changed although considered Stable Disease according to RECIST<sup>15</sup>, whereas the SUV values of the same lesions were slightly reduced, during the year when Patient LRW received CPI-613 therapy during the trial. The non-target lesion (also defined according to RECIST<sup>15</sup>) remained stable during the entire year of CPI-613 therapy. After her participation in the CL-CPI-613-002 trial, Patient LRW was on maintenance therapy with CPI-613. RML = right middle lobe.



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