

## CASE REPORT

# Everolimus and Octreotide in a Patient with High-Grade Pancreatic Neuroendocrine Carcinoma

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### ABSTRACT

**Context** Pancreatic Neuroendocrine Tumors are overall rare tumors with a poor prognosis. Treatment options for high grade pancreatic neuroendocrine tumors are limited especially for those with progressive disease. Everolimus, an oral inhibitor of mammalian target of rapamycin, has been approved for the treatment of patients with low- or intermediate-grade advanced pancreatic neuroendocrine tumor. **Case report** Herein we present a case of a 52-year-old patient who has been diagnosed with Stage IV, high-grade large-cell neuroendocrine carcinoma of the pancreas with liver and lung metastases. The patient first treated with cisplatin and etoposide for six cycles; then his disease progressed after a year of observation. As a result, he was treated with capecitabine and temozolomide as a second line treatment for seven cycles until he experienced significant toxicity and the treatment was stopped. Subsequently, the treatment with everolimus and octreotide long-acting release combination was started. Our patient achieved a long-term survival benefit for 52 months and prolonged clinical response to third line everolimus plus octreotide for more than 28 months. **Conclusion** This case demonstrates activity of the combination of everolimus plus octreotide long-acting release, and warrants further evaluation in large cell neuroendocrine tumors.

### INTRODUCTION

Pancreatic Neuroendocrine Tumors (PNETs) are overall rare tumors with incidence of  $\leq 1$  case per 100,000 individuals per year and account for 1 to 2 percent of all pancreatic tumors [1, 2, 3]. The incidence and prevalence of PNET in the United States and elsewhere have increased likely due to detection of asymptomatic disease on cross-sectional imaging and endoscopy done for other indications [3, 4]. The World Health Organization (WHO) classifies neuroendocrine neoplasm arising within the digestive system, according to proliferative rate, into two broad categories. Well-differentiated neuroendocrine tumors (Ki-67  $<20\%$ ), this category is further separated, into low-grade (Ki-67  $<3\%$ ), intermediate-grade (Ki-67 = 3 to 20%) and poorly differentiated high-grade neuroendocrine carcinomas (Ki-67  $>20\%$ ) [5].

Prognosis for unresectable PNETs is generally poor when compared to classic carcinoid of the small bowel;

however, the histological grade can affect the prognosis where 5-year survival rates for low-, intermediate-, and high-grade tumors are 75%, 62%, and 7%, respectively. When considered based on stage of disease per American Joint Committee on Cancer (AJCC) classification, 5-year overall survival (OS) rates for stages I, II, III, and IV were 92%, 84%, 81%, and 57%, respectively [6].

The current guidelines for the management of well-differentiated metastatic PNETs recommend streptozocin plus 5-fluorouracil/doxorubicin or, temozolomide, with or without capecitabine, as chemotherapy, and everolimus or sunitinib as targeted agents [7, 8, 9, 10, 11, 12, 13]. There is a general lack of data from prospective trials to guide clinical decision-making regarding treatment of high-grade metastatic PNETs. Current treatment approaches include chemotherapy that is based on the pattern of small cell lung cancer with cisplatin and etoposide. Alternative regimens substituting carboplatin for cisplatin or irinotecan for etoposide have been validated in metastatic small-cell lung cancer and are therefore thought to be acceptable options [14, 15]. Temozolomide-based chemotherapy is commonly used as a second-line treatment [16].

Everolimus, an orally administered mammalian target of rapamycin (mTOR) inhibitor, has demonstrated anti-tumor activity in patients with low- or intermediate-grade PNET who have experienced treatment failure with prior chemotherapy [17]. Subsequently, further investigation in this patient group was initiated with the prospective, randomized, phase III RADIANT-3 trial. RADIANT-3 was

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conducted to assess the efficacy and safety of everolimus compared with placebo among patients with low- or intermediate-grade PNETs and radiologic documentation of disease progression. Results showed that the median progression-free survival to be significantly longer among PNETs patients who received everolimus than among those with Placebo [11.0 vs. 4.6 months; hazard ratio, 0.35; 95% confidence interval (CI), 0.27–0.45;  $p < 0.001$ ]. Stable disease was observed in 73% of everolimus-treated patients compared with 51% of those receiving placebo, and tumor shrinkage was also greater in the everolimus arm (64%) compared with the placebo arm (21%). Everolimus was generally well tolerated; adverse events were mostly graded 1 or 2 in severity, consistent with known mTOR side effects, and generally reversible [18]. Median OS was 44.0 months for those randomly assigned to everolimus and 37.7 months for those assigned to placebo, although this finding was not statistically significant; crossover of patients likely confounded the OS results [19]. Also, everolimus has been reported to have activity in progressive metastatic medullary thyroid cancer in a case report [20]. On the other hand, the multitargeted tyrosine kinase inhibitor sunitinib has also shown activity against pancreatic neuroendocrine tumors; it was compared with placebo in a phase III trial. Median PFS was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group [21]. In a later report, median overall survival favored sunitinib (38.6 vs 29.1 months), but the difference was not statistically significant, potentially due to crossover from placebo to sunitinib in 69 percent of the control group [22]. Herein, we present a case of Stage IV, high-grade pancreatic large-cell neuroendocrine carcinoma who achieved long term survival benefit and prolonged clinical response for more than 28 months to everolimus plus octreotide as a third line treatment.

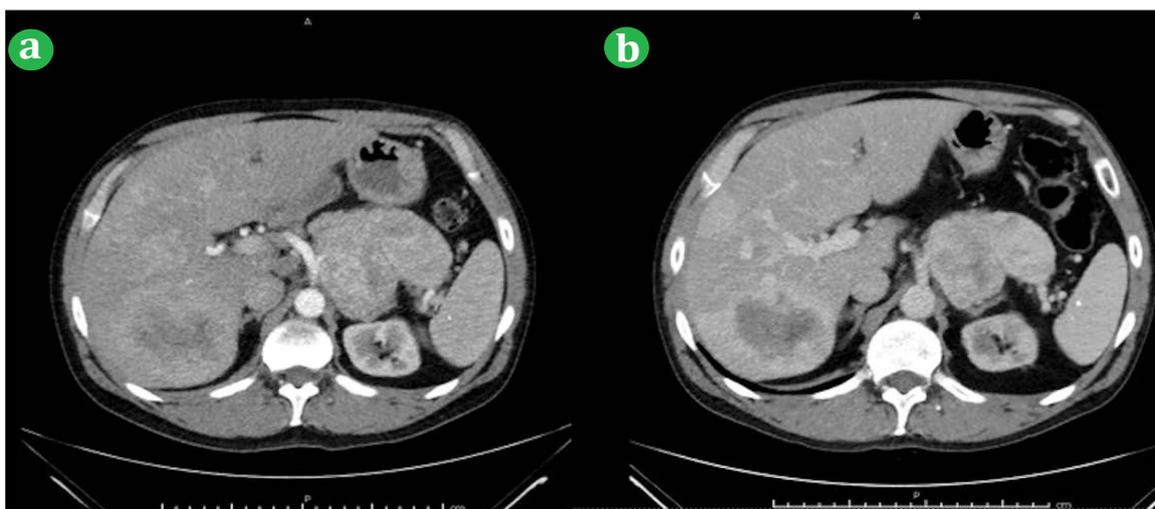
## CASE REPORT

In April 2013, a fifty-two-year-old man presented with four months' history of Gastroesophageal reflux disease (GERD) symptoms that are not relieved with prescription medications of proton pump inhibitors (PPI). Computed tomography (CT) scan of the abdomen, pelvis and chest revealed a 5×8 cm lobulated mass in the body and the tail of the pancreas with enlarged peri-pancreatic lymph nodes that occluded the splenic vein, a numerous hypervascular lesions throughout the hepatic parenchyma (the largest lesion measured approximately 9 cm in diameter) and two dominant left lower lobe pulmonary nodules measuring up to 1.5 cm. The patient underwent Fine Needle Aspiration (FNA) of the liver lesion which showed sheets of loosely cohesive malignant cells exhibiting significant cellular and nuclear pleomorphism with numerous bizarre forms, many cells were multinucleated and contained intranuclear and cytoplasmic vacuoles. The tumor cells were positive for cytokeratin, synaptophysin and weakly positive for chromogranin, Ki-67 proliferative index stains approximately 35% of tumor cells. CK7, CK20, TTF1, CDX2 and S100 were all negative.

As a part of his work up he did have tumor markers done and of significance, his CA-19-9 was 10 (range: 0-37 U/ml), and Chromogranin A was 2778 (range: 0-93 ng/ml). Octreotide scintigraphy revealed increased focal activity in the pancreatic mass, liver parenchyma, and in the left lower lobe. These findings were consistent with the diagnosis of Stage IV, high grade large-cell neuroendocrine carcinoma of the pancreas with liver and lung metastases. Platinum based chemotherapy was initiated in April 2013 (Cisplatin at 75 mg/m<sup>2</sup> on day 2 and Etoposide at 100 mg/m<sup>2</sup> on day 1 through day 2) with pegfilgrastim support for six cycles until August 2013 when his CT scans showed stable disease and the patient was followed up every three months. Later in August 2014, the patient presented with increased reflux symptoms and right upper quadrant abdominal pain. As a result, he underwent further workup, which showed disease progression, as assessed by CT scans and serum markers. Gastrin and chromogranin A were measured at 917 pg/mL (range: 0-100 pg/ml), and 8240 ng/mL, respectively. Subsequently, second line treatment with capecitabine (1000 mg/m<sup>2</sup> on days 1–14 on every 28-day basis) and temozolomide (200 mg/m<sup>2</sup> on days 10–14 on every 28-day basis) was initiated, however after 7 cycles the patient experienced significant peripheral neuropathy and fatigue and the treatment was discontinued with radiologic imaging showed stable disease (**Figure 1a**). Considering the initial data findings from the recent RADIANT-3 study and the patient's excellent performance status, he was started on everolimus (10 mg/day) plus octreotide LAR (20 mg every 4 weeks) in February 2015 after obtaining informed consent from the patient per institution standard of care. His chromogranin A concentration was 5948 ng/ml and Gastrin concentration was 674 ng/ml. Six months after starting everolimus plus octreotide LAR, his chromogranin A and gastrin concentration decreased to 950 ng/mL and 264 pg/mL respectively, with radiologic images showing stable disease. In June 2017, after 28 months of everolimus plus octreotide LAR as third-line therapy, the patient continued to be asymptomatic and had ECOG score of 1. His CT scans revealed stable pancreatic mass, liver metastasis (**Figure 1b**) and lung nodules. Chromogranin A of 868ng/mL and gastrin of 437 pg/mL level. Throughout the course of everolimus plus octreotide LAR treatment, the patient maintained an excellent quality of life with minor treatment-related toxicities including grade 1 fatigue, diarrhea, and occasional mucositis. He continued to work full time and was able to meet his first grandchild during this period.

## DISCUSSION

In this case, we report activity of everolimus in a patient with large cell pancreatic neuroendocrine carcinoma and high Ki67 (35%) who progressed after cytotoxic chemotherapy and achieved a very prolonged stable disease. Because of the activity of the mTOR pathway in the pathogenicity of PNET, everolimus has been investigated as a second line therapy in patients with advanced disease with evidence activity leading to



**Figure 1.** Treatment outcome for a patient with stage IV, high grade large-cell neuroendocrine carcinoma of the pancreas with liver and lung metastases. **(a).** Abdominal CT scan showing pancreatic mass with liver metastases before starting everolimus plus octreotide treatment. **(b).** CT scan after 28 months of follow-up showing a stable disease.

its evaluation and later approval in 1<sup>st</sup> line settings. The activity of everolimus was evaluated in patients with well and moderately differentiated PNET, and in the pivotal study 82% had well differentiated disease. The high Ki-67 level and the histology of large cell carcinoma represent poor risk features with poor prognosis and median survival of 21 months [6]. Our case raises the question whether there is an activity of mTOR pathway inhibitors even in large cell neuroendocrine tumors, and whether Ki67 as a marker should be the determining factor for trial enrollment as opposed to more modern genomic signature. In the case presented here, a patient with high-grade, stage IV large-cell pancreatic neuroendocrine carcinoma was treated with multiple lines of treatments and achieved long-term survival for more than 52 months and reduction in disease biomarkers. The combination of everolimus plus octreotide LAR demonstrated markedly improved clinical response and an addition of 28 months of progression-free survival. The clinical and radiologic benefits were unexpected considering that a poor prognosis features existed given the disease stage, high-grade tumor and two failed prior lines of therapies. Our patient tolerated everolimus plus octreotide LAR very well with manageable toxicity (grade 1: rash, mouth sores, nail changes, nasal bleeding, diarrhea).

## CONCLUSION

In summary, this case report suggests that the combination of everolimus plus octreotide LAR may offer a valuable treatment strategy for patients with heavily pretreated, advanced, high-grade pancreatic neuroendocrine tumors and warrant further investigation of this regimen. Randomized phase III studies remain the gold standard to determine the efficacy of such a regimen.

## Conflict of Interest

The authors have declared that no competing interests exist.

## References

1. Kloppel G, A Perren, PU Heitz. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci* 2004; 1014:13-27. [PMID: 15153416]
2. Klimstra DS. Nodular neoplasms of the pancreas. *Mod Pathol* 2007; 20:S94-112. [PMID: 17486055]
3. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; 121:589-97. [PMID: 25312765]
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; 26:3063-72. [PMID: 18565894]
5. Rindi G, Arnold R, Bosman FT. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, et al., editors. WHO classification of tumors of the digestive system. Lyon: IARC; 2010.
6. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK, et al. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol* 2011; 29:3044-9. [PMID: 21709192]
7. Oberg K, Akerstrom G, Rindi G, Jelic S. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21:223-7. [PMID: 20555086]
8. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 2004; 22:4762-71. [PMID: 15570077]
9. Delaunoy T, Ducreux M, Boige V, Dromain C, Sabourin JC, Duvillard P, et al. The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma; a judicious option? *Eur J Cancer* 2004; 40:515-20. [PMID: 14962717]
10. Kulke MH, Bendell J, Kvols L, Picus J, Pommier R, Yao J. Evolving diagnostic and treatment strategies for pancreatic neuroendocrine tumors. *J Hematol Oncol* 2011; 4:29. [PMID: 21672194]
11. Eriksson B, Annibale B, Bajetta E, Mitry E, Pavel M, Platania M, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: chemotherapy in patients with neuroendocrine tumors. *Neuroendocrinology* 2009; 90:214-9. [PMID: 19713713]
12. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 2011; 117:268-75. [PMID: 20824724]

13. Krug S, Boch M, Daniel H, Nimphius W, Müller D, Michl P, et al. Streptozocin-Based Chemotherapy in Patients with Advanced Neuroendocrine Neoplasms-Predictive and Prognostic Markers for Treatment Stratification. *PLoS One* 2015; 10:e0143822. [PMID: 26630134]
  14. Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas* 2010; 39:799-800. [PMID:20664477]
  15. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013; 24:152-60. [PMID: 22967994]
  16. Welin S, Sorbye H, Sebjornsen S, Knappskog S, Busch C, Oberg K. Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. *Cancer* 2011; 117:4617-22. [PMID: 21456005]
  17. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 2008; 26:4311-8. [PMID: 18779618]
  18. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364:514-23. [PMID: 21306238]
  19. Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. *J Clin Oncol* 2016. [PMID: 27621394]
  20. Faggiano A, Ramundo V, Dicitore A, Castiglioni S, Borghi MO, Severino R, et al. Everolimus is an active agent in medullary thyroid cancer: a clinical and in vitro study. *J Cell Mol Med* 2012; 16:1563-72. [PMID: 21883896]
  21. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364:501-13. [PMID: 21306237]
  22. Faivre S, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL et al. Sunitinib in Pancreatic Neuroendocrine Tumors: Updated Progression-Free Survival and Final Overall Survival From a Phase III Randomized Study. *Ann Oncol* 2016. [PMID: 27836885]
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