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Update on Diagnosing and Treating Pancreatic Neuroendocrine Tumors (pNETs)

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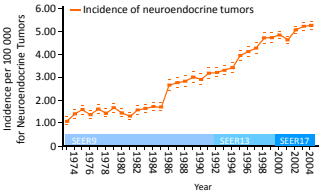
Neuroendocrine Tumors: Incidence and Prevalence

- Early estimates of incidence 1-2 per 100,000 population[1]
- Diagnosed incidence increasing, likely due to improved awareness, classification, and diagnostic modalities[2]
- Prevalence estimated to be >100,000 in United States



Cases selected from SEER database (1973 to 2004) using International Classification of Disease for Oncology histology codes 8150 to 8157, 8240 to 8246, and 8249.

1. Modlin et al. *Cancer* 2003; 97: 934-59
2. Yao et al. *J Clin Oncol* 2008;26:3063-3072

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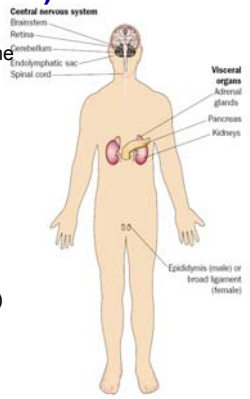
von Hippel-Lindau (vHL)

Autosomal Dominant Tumor Syndrome
VHL tumor suppressor gene - 3p25

Predisposes individuals to:

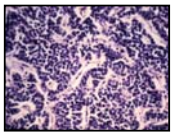
- Hemangioblastomas – CNS (44-72%)
- Hemangioblastomas – retina (25-60%)
- Endolymphatic sac tumors (10%)
- Epididymal cystadenoma (25-60%)
- Renal Cell Carcinoma (25-60%)
- Pheochromocytoma (10-20%)
- Pancreatic lesions (35-70%)

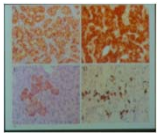


Neuroendocrine Tumors: Clinical Features

- "Well differentiated" with rare mitoses
- Pursue indolent clinical course: median survival of patients with metastatic disease may exceed 5 years
- Ability to secrete neuropeptides, resulting in characteristic clinical syndromes

"Well differentiated neuroendocrine tumor"





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Pancreatic Lesions in vHL

- **Cysts- 70%**
  - **Single or multiple**
  - **No malignant potential**
  - **Can lead to pancreatic insufficiency**
- **Neuroendocrine tumors- 12-17%**
  - **Non-functional in our series**
  - **Metastases seen in 8% of these patients**
    - **Previous studies have shown size to be predictive of metastatic potential**

Libutti et al. Surgery 1998
Libutti et al. Surgery 2000

CT Appearance of PNET

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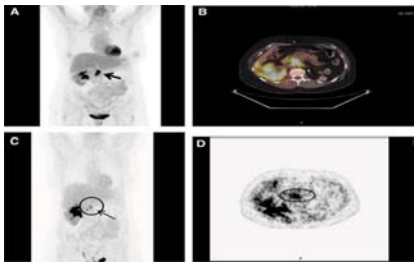
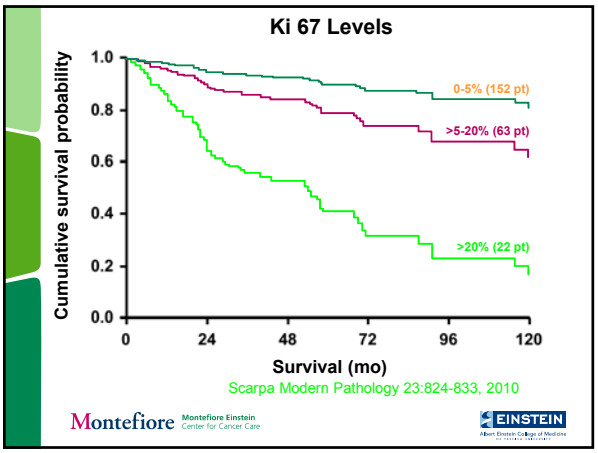


Fig 2 Example of an <ce:sup loc="pre"> 18</ce:sup> F-FDG and <ce:sup loc="pre"> 18</ce:sup> F-DOPA avid lesion in the uncinate process of the pancreas from the same patient. <ce:italic> A</ce:italic> , Scout image of the <ce:sup loc="pre"> 18</ce...
Mio Kitano , Corina Millo , Reza Rahbari , Peter Herscovitch , Krisana Gesuwan , Richard C. Webb , Aradhana M. Ve...

Comparison of 6-<ce:sup loc="pre">18</ce:sup>F-Fluoro-<ce:small-caps>l</ce:small-caps>-DOPA, <ce:sup loc="pre">18</ce:sup>F-2-deoxy-<ce:small-caps>d</ce:small-caps>-glucose, CT, and MRI in patients with pancreatic neuroendocrine neoplasms with von Hippel-Lindau disease
Surgery Volume 150, Issue 6 2011 1122 - 1128

http://dx.doi.org/10.1016/j.surg.2011.09.048



Pancreatic NETs

Staging: Mod ENETS-TNM (N=274)*

Tumor Staging	Stage
•T1 <2 cm	I T1-2 (ltd panc, <4 cm)
•T2 2-4	II T3 (ltd panc, > 4 cm)
•T3 >4 (ltd pancreas)	III T4 or N1 (outside pancreas
•T4 (beyond pancreas)	IV M1

*Scarpa Modern Pathology 23:824-833, 2010

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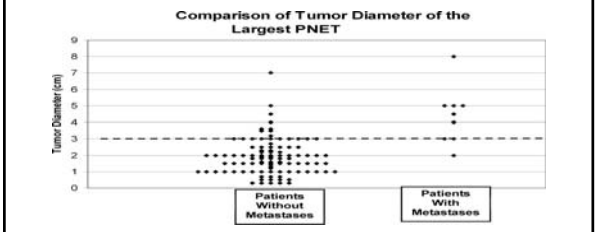


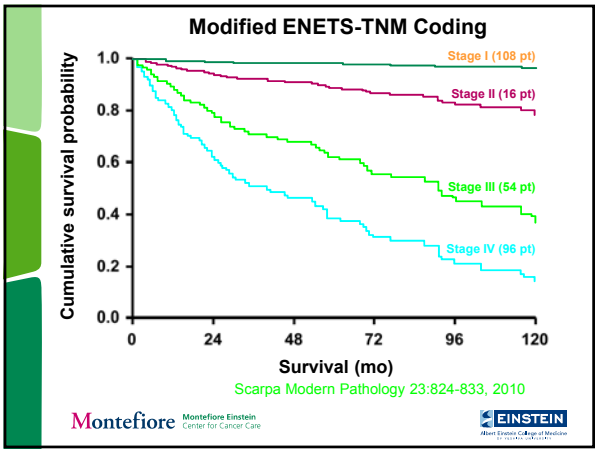
Fig 1 Scatterplot of the neoplasm diameters of primary PNETs to compare patients with and without metastatic disease; 67% of patients with metastatic disease (6/9 patients) compared with 19% of patients without metastatic disease (19/99 patients)...

Joseph A. Blansfield , Lynda Choyke , Shane Y. Morita , Peter L. Choyke , James F. Pingpank , H. Richard Alexander...

Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine tumors (PNETs)

Surgery Volume 142, Issue 6 2007 814 - 818.e2

http://dx.doi.org/10.1016/j.surg.2007.09.012



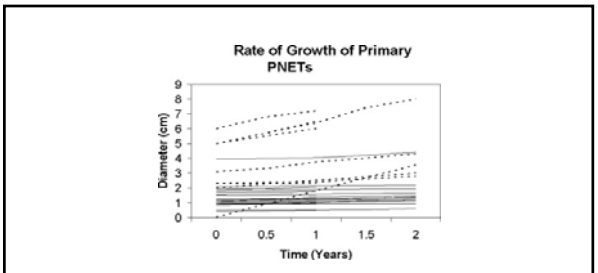


Fig 2 Rate of growth of the diameter of the primary PNET in patients with vHL. Dashed lines are growth rates for individuals who had metastatic disease; solid lines are growth rates for individuals without metastases.

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Comparison of Patients With and Without Metastatic Disease from PNETs

	Metastatic Disease Present (Total)	Metastatic Disease Absent (Total)	P value
Male (Total)	2 (9)	49 (99)	<0.16
Size >3	6 (9)	19 (99)	<0.0046
>1 Primary Lesion	5 (9)	27 (99)	<0.12
Location of Primary in the Head of Pancreas	8 (9)	75 (99)	<0.15
Exon 3 Mutation Present	7 (9)	32 (99)	<0.01
Mean doubling time (range)	337 days (9) (180-463)	2628 days (54) (103-9614)	<0.0001

Tumor Doubling available for 9/9 pts with metastatic disease and 54/99 pts without

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Tumor sizes available for 9/9 pts with metastatic disease and 54/99 pts without

Comparison of Patients With and Without Metastatic Disease from PNETs

Criteria: 1) Exon 3 mutation
2) Diameter of pancreatic lesion ≥3cm
3) Doubling time <500days

No. of Criteria Met	No. of Pts with Metastatic Disease	No. of Pts. without Metastatic Disease
0 out of 3	0	29
1 out of 3	0	20
2 out of 3	3	5
3 out of 3	6	0

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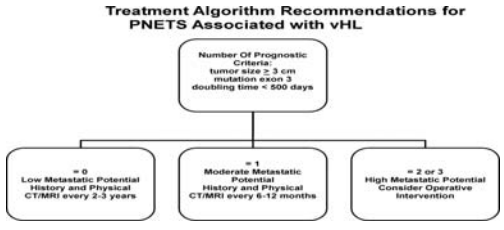

Fig 3 Treatment and follow-up recommendations for patients with PNETs.

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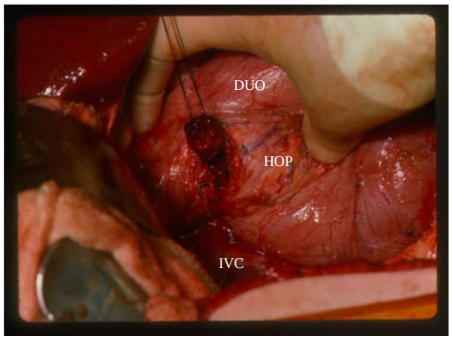
Enucleation of PNET



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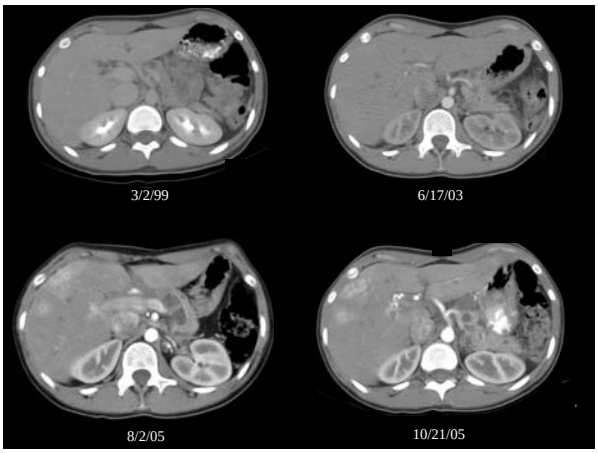

Malignant Neuroendocrine Tumors

Well-Differentiated Pancreatic Endocrine Neoplasms

Patients: n=183, (166 rendered NED at surgical resection)

Hepatic Recurrence (first site): n=22 (76%) (Ferrone/Allen, MSKCC: JCO 2007 (25):5609)

Non-Functional PNET

2.6-3.0 cases/million population

At diagnosis: Node +: 44%, Metastatic Disease: 60%

Median Survival M+ Disease: 1.4 years (Franko/Moser, UPMC: AHPBA 2008)

Carcinoid Tumors

38.4 cases/million US population (increasing)

Presence of metastatic disease varies with tumor size.

Hepatic metastases will occur in 30 to 50% of patients with tumors >2cm

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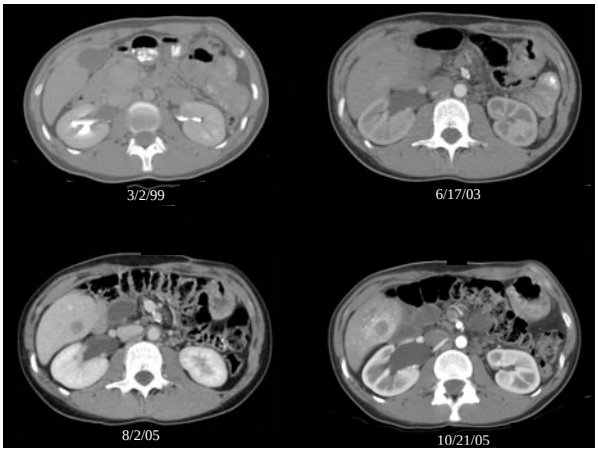

Ann Surg Oncol (2010) 17:3129–3136
DOI 10.1245/s10434-010-1154-5

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Surgical Management of Hepatic Neuroendocrine Tumor Metastasis: Results from an International Multi-Institutional Analysis

Skye C. Mayo, MD, MPH[1], Mechteld C. de Jong, MD[1], Carlo Pulitano, MD[2], Brian M. Clary, MD[3], Srinevas K. Reddy, MD[3], T. Clark Gamblin, MD, MS[4], Scott A. Celinksi, MD[4], David A. Kooby, MD[5], Charles A. Staley, MD[5], Jayme B. Stokes, MD[5], Carrie K. Chu, MD[5], Alessandro Ferrero, MD[6], Richard D. Schulick, MD[1], Michael A. Choti, MD[1], Giles Mentha, MD[6], Jennifer Strub, MD[6], Todd W. Bauer, MD[7], Reid B. Adams, MD[7], Luca Aldrighetti, MD[2], Lorenzo Capussotti, MD[8], and Timothy M. Pawlik, MD, MPH[1]

[1]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Ospedale San Raffaele, Milan, Italy; [3]Duke Medical Center, Durham, NC; [4]University of Pittsburgh, Pittsburgh, PA; [5]Emory University School of Medicine, Atlanta, GA; [6]Hôpitaux Universitaires de Genève, Geneva, Switzerland; [7]University of Virginia, Charlottesville, VA; [8]Ospedale Mauriziano Umberto I, Turin, Italy

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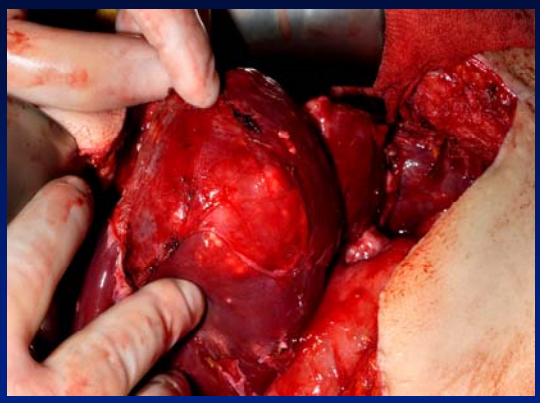

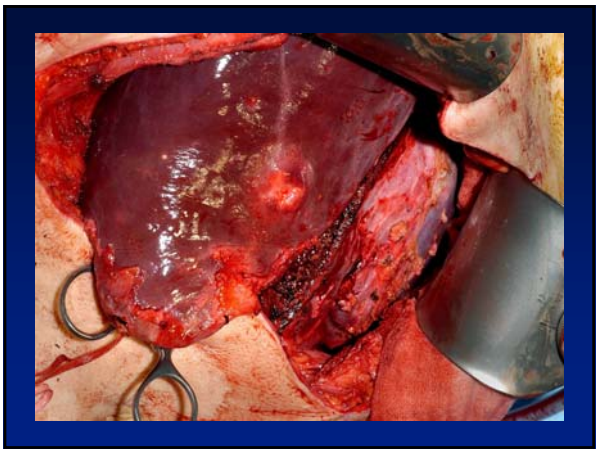

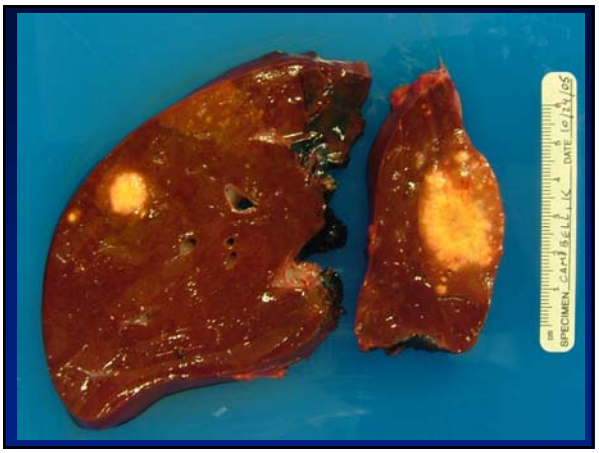

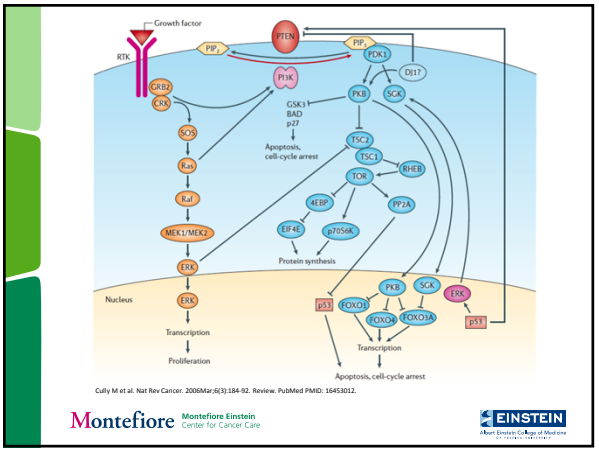

Cully M et al. Nat Rev Cancer. 2006Mar;6(3):184-92. Review. PubMed PMID: 16453012.

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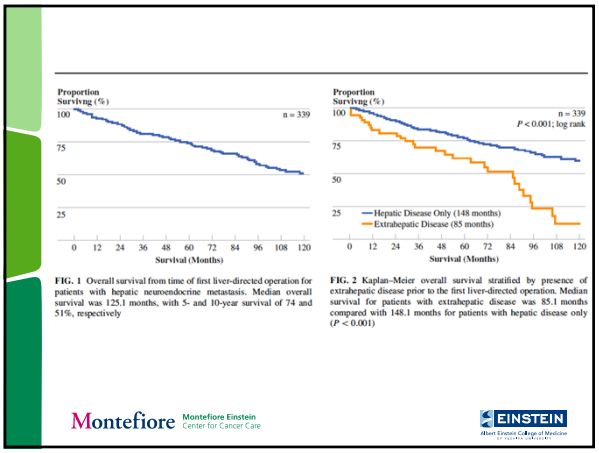

FIG. 1 Overall survival from time of first liver-directed operation for patients with hepatic neuroendocrine metastasis. Median overall survival was 125.1 months, with 5- and 10-year survival of 74 and 51%, respectively

FIG. 2 Kaplan-Meier overall survival stratified by presence of extrahepatic disease prior to the first liver-directed operation. Median survival for patients with extrahepatic disease was 85.1 months compared with 148.1 months for patients with hepatic disease only ($P < 0.001$)

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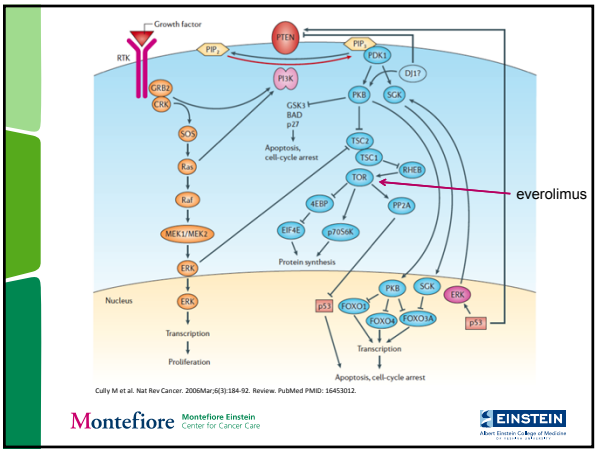

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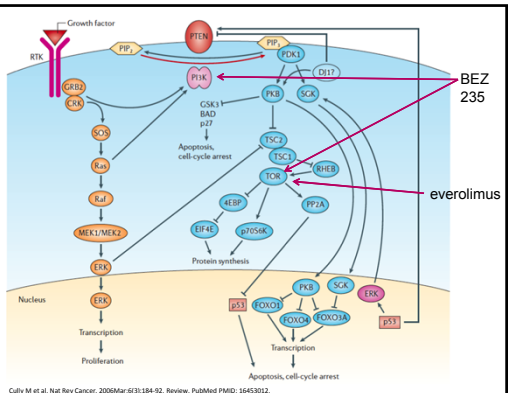

Cully M et al. Nat Rev Cancer. 2006Mar;6(3):184-92. Review. PubMed PMID: 16453012.

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E2212: A randomized, double-blinded, placebo-controlled Phase II study of adjuvant everolimus following the resection of metastatic pancreatic neuroendocrine tumors to the liver

Steven K. Libutti (PI)
Pamela L. Kunz (Co-PI)
Yoko Franchetti (ECOG Statistician)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

ABSTRACT

BACKGROUND

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors, in two phase 2 studies. We evaluated the agent in a prospective, randomized, phase 3 study.

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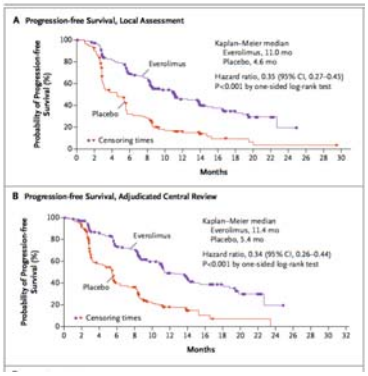
Background

- Cytoreductive strategies (ie. hepatic resection or ablation) for advanced pNET improve overall survival. [1-4]
- For patients undergoing an R0 or R1 resection of liver metastases, median RFS is 15 months. Yet, the majority of patients recur (94% at 5 years). [1]
- Everolimus confers a statistically significant 6-month prolongation in PFS compared to placebo in advanced pNETs (4.0 vs. 11.0 months)[5]

1. Mayo, Annals Surg Onc. 2010. 2. Elias, Surgery. 2003. 3. Knigge, Surgeon. 2008. 4. Yao, Surgery. 2001. 5. Yao, NEJM. 2011.



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Schema and Study Design

Low and intermediate grade advanced pNETs following R0 or R1 resection of hepatic metastases n=150

RANDOMIZE

Everolimus 10 mg po daily for 12 months n=75

Placebo po daily for 12 months n=75

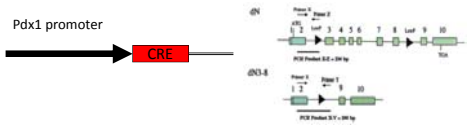
*No crossover allowed

- Primary Endpoint: RFS (response assessment Q 3 months)
- Secondary Endpoints: OS, toxicity, quality of life assessment
- Stratification (to ensure balance between arms):
  - –R0 vs. R1 resection
  - –Primary tumor resected with metastectomy vs. primary tumor tumor resected prior to metastectomy

Key Eligibility Criteria

- Patients with metastatic low or intermediate grade pancreatic neuroendocrine tumors to the liver who recovered from an R0 or R1 resection of all disease (including resection of a primary PNET if present) or resection plus microwave or radiofrequency ablation to R0 or R1 status
- Tissue available for central review to be done after patient enrollment not for eligibility (to include Ki-67 and mitotic index, NANETS grading system will be employed core biopsy preferred over FNA)
- Prior treatment with sunitinib and/or cytotoxic chemotherapy are allowed; no prior everolimus.
- ECOG performance status ≤ 2.

Pancreatic Specific Inactivation of Men1



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Developing Mouse Models of Endocrine Neoplasms

Tissue specific mouse "knockout" using <u>Cre/lox</u> system

- Pancreatic specific Cre line

Inactivation of tumor suppressor genes in pancreas

- von Hippel Lindau (*Vhl*)
- Multiple Endocrine Neoplasia Type 1 (*Men1*)

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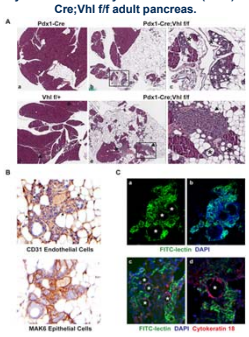
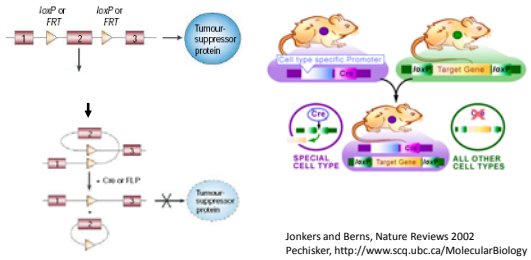
Figure 4. Histological analysis of the microcystic adenomas (MCA) which developed in Pdx1-Cre;Vhl f/f adult pancreas.



Shen H-CJ, Adem A, Ylaya K, Wilson A, et al. (2009) Deciphering von Hippel-Lindau (VHL/Vhl)-Associated Pancreatic Manifestations by Inactivating Vhl in Specific Pancreatic Cell Populations. PLoS ONE 4(4): e4897. doi:10.1371/journal.pone.0004897
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0004897

PLoS one

Cre/LoxP System



Jonkers and Berns, Nature Reviews 2002
Pechisker, http://www.scq.ubc.ca/MolecularBiology

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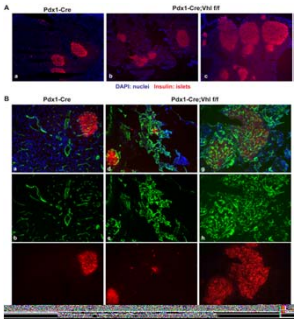
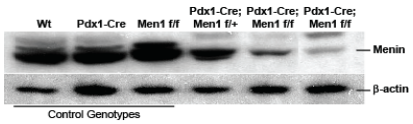
Figure 5. Histological analysis of the endocrine pancreas in Pdx1-Cre;Vhl f/f mice.



Shen H-CJ, Adem A, Ylaya K, Wilson A, et al. (2009) Deciphering von Hippel-Lindau (VHL/Vhl)-Associated Pancreatic Manifestations by Inactivating Vhl in Specific Pancreatic Cell Populations. PLoS ONE 4(4): e4897. doi:10.1371/journal.pone.0004897
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0004897

PLoS one

Decreased Menin Protein Expression in Pdx1-Cre; Men1 f/f Pancreas



Total protein lysate from 12 month old mouse pancreas

Shen HC, He M, Powell A, Adem A, Lorang D, Heller C, Grover AC, Ylaya K, Hewitt SM, Marx SJ, Spiegel AM, Libutti SK. Recapitulation of Pancreatic Neuroendocrine Tumors in Human Multiple Endocrine Neoplasia Type I Syndrome via Pdx1-Directed Inactivation of Men1. Cancer Res. 2009 Feb 10. [Epub ahead of print] PMID: 19208834

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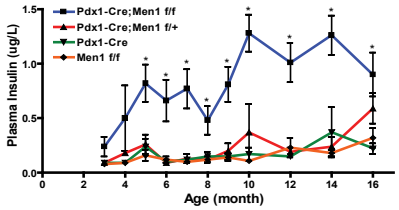
Elevated Plasma Insulin in Pdx1-Cre;Men1 f/f



Number of animals represented in graphs

Age (month)	3	4	5	6	7	8	9	10	12	14	16
Pdx;Men1 f/f	9	9	11	10	13	11	9	6	9	6	4
Pdx;Men1 f/+	8	10	7	5	8	7	6	4	8	5	5
Pdx	9	10	9	9	10	9	9	5	9	6	5
Men1 f/f	5	6	8	7	8	7	5	3	6	6	5
total	31	35	35	31	41	34	29	18	32	23	19
p-values	0.0651	0.1450	0.0011	0.0029	0.0002	0.0125	0.0001	0.0003	0.0001	0.0003	0.0097

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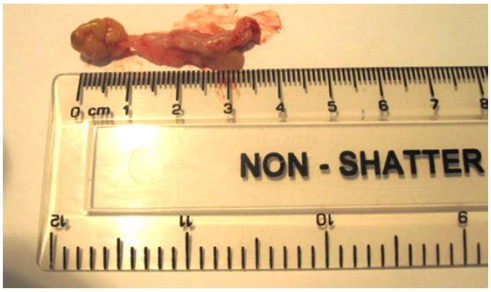

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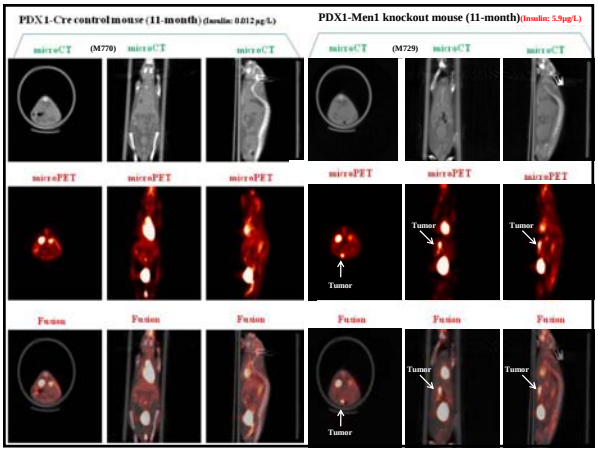
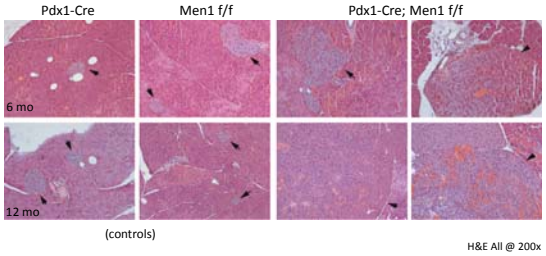


Development of Neuroendocrine Tumors in Pdx1-Cre;Men1 f/f Pancreas



(controls)

H&E All @ 200x

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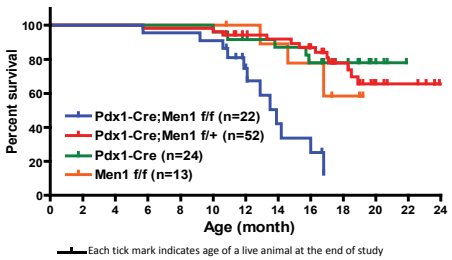
Reduced Life Expectancy in Pdx1-Cre;Men1 f/f



Each tick mark indicates age of a live animal at the end of study

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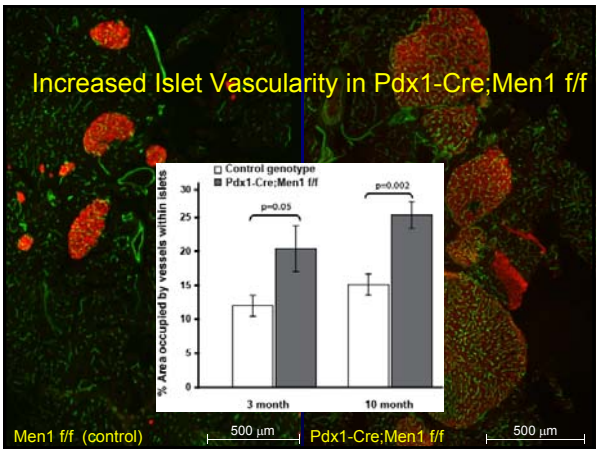

Inhibition of VEGF Signaling in Mouse Model of MEN1 Insulinoma

Experimental design

- Sunitinib: a small-molecule multiple receptor tyrosine kinase inhibitor, that inhibits all known PDGF and VEGF receptors
- Treatment regimen: daily oral gavage of sunitinib (20mg/kg) for 3 months
- Genotypes: Pdx1-Cre;Men1 f/f and Men1 f/f
- Groups: Treatment vs. vehicle within each genotype
- Variables: Age (3-4 month), sex, weight matched within each genotype

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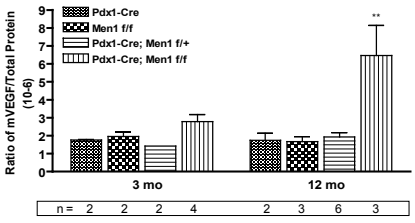
Upregulated VEGF Expression in Pdx1-Cre;Men1 f/f Pancreas



VEGF ELISA using total pancreatic lysate

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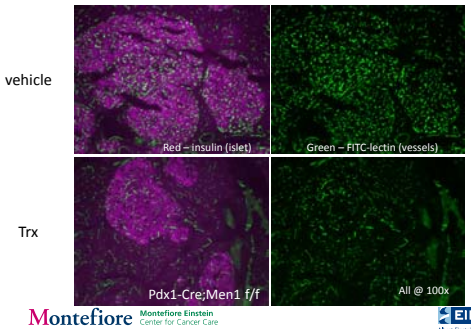
Islet Vascularity in Pdx1-Cre; Men1 f/f Pancreas



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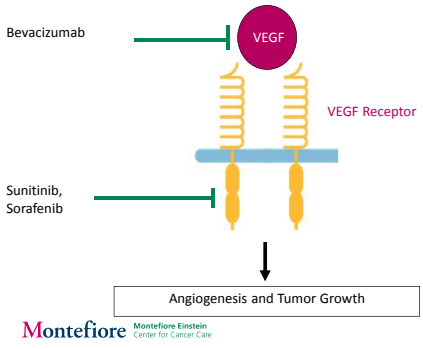
Targeting the VEGF Pathway in Neuroendocrine Tumors



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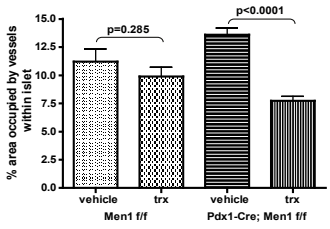
Significant Reduction in Islet Vascularity



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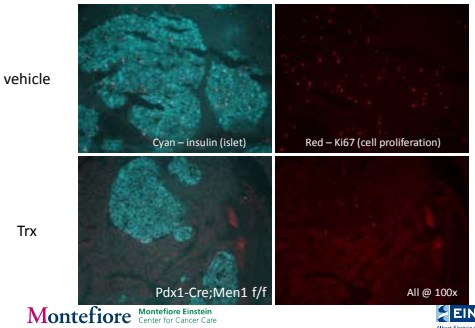
Cell Proliferation in Pdx1-Cre;Men1 f/f Pancreas



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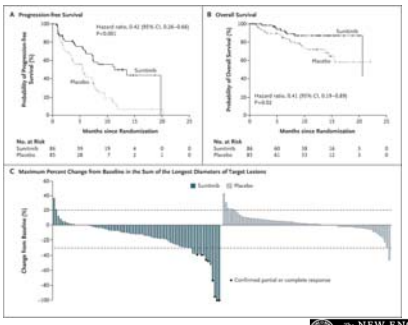
Kaplan-Meier Analysis of Progression-free Survival and Overall Survival in the Intention-to-Treat Population and the Maximum Percent Change from Baseline in the Sum of the Longest Diameters of Target Lesions, According to Patient.



Raymond E et al. N Engl J Med 2011;364:501-513.

The NEW ENGLAND JOURNAL of MEDICINE

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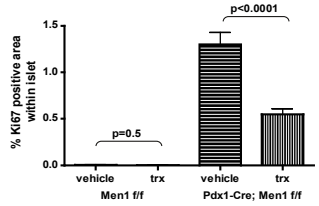
Significant Decrease In Islet Cell Proliferation



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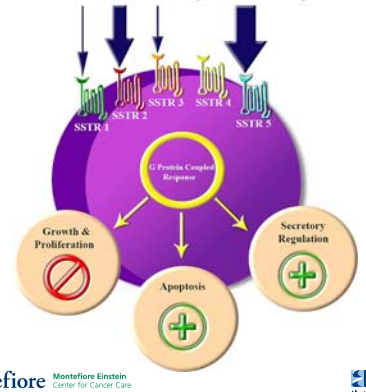
Pasireotide (SOM230)



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ORIGINAL ARTICLE

A Correction Has Been Published

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

N Engl J Med 2011; 364:501-513 | February 10, 2011

We conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. All patients had Response Evaluation Criteria in Solid Tumors–defined disease progression documented within 12 months before baseline. A total of 171 patients were randomly assigned (in a 1:1 ratio) to receive best supportive care with either sunitinib at a dose of 37.5 mg per day or placebo. The primary end point was progression-free survival; secondary end points included the objective response rate, overall survival, and safety.

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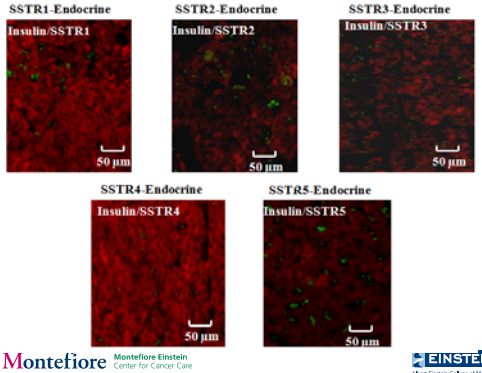
$SSTR_{1-5}$ expressed in insulinomas of *Men1* KO mice



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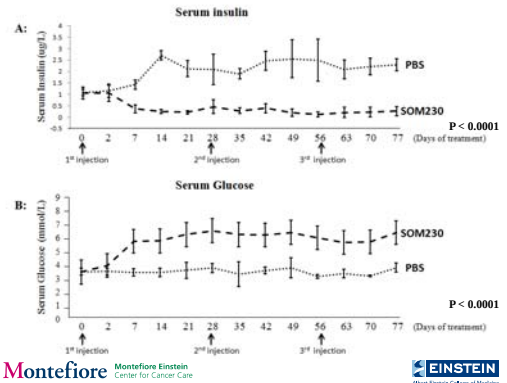
Serum insulin and glucose analysis



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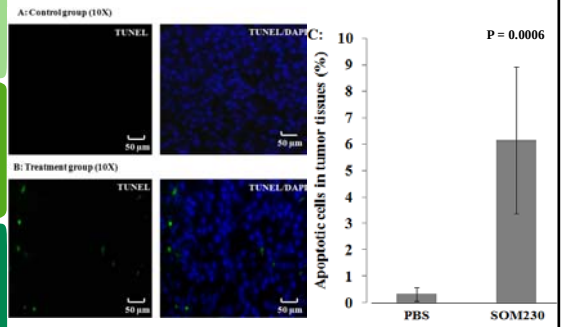
TUNEL Assay: ↑Apoptosis



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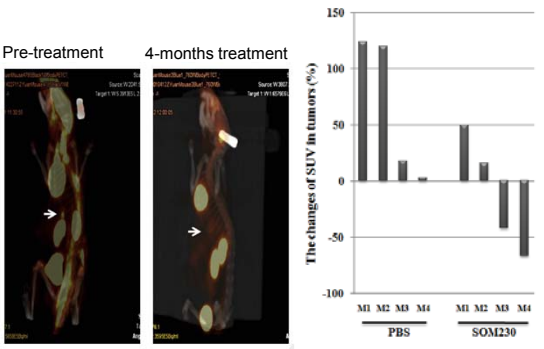
microPET/CT Analysis: ΔSUV_{max}



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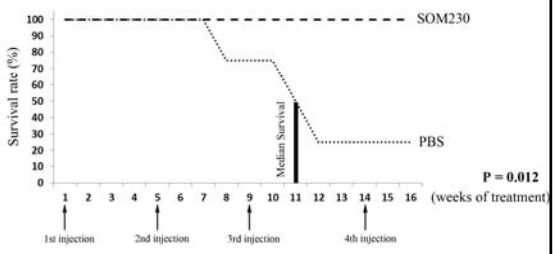
Increased Survival



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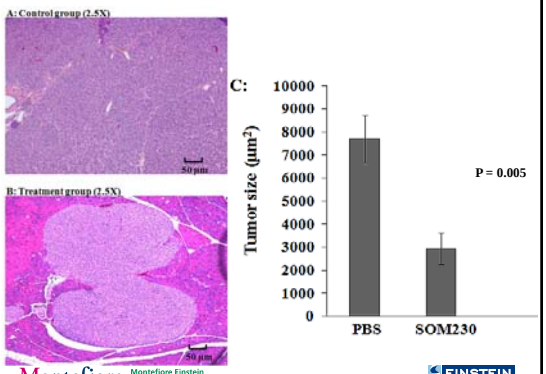
Morphometric analysis: ↓ Tumor Size



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Currently Open and Pending Clinical Trials

- ZEBRA – Novartis Oncology
  Randomized trial comparing everolimus to BEZ for patients with stage IV PNET
- Randomized trial comparing BEZ to placeco for patients with stage IV PNET
- 718-862-8840
  Steven Libutti, Monique White, Stella Forbes

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Conclusions

- Neuroendocrine Tumors represent a diverse group of neoplasms.
- Management strategies need to address the unique pathways involved in tumor progression.
- Mouse models can be informative in the development of new treatment strategies.

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