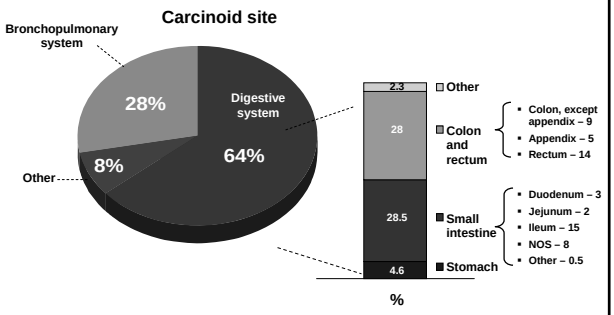
Neuroendocrine Tumors

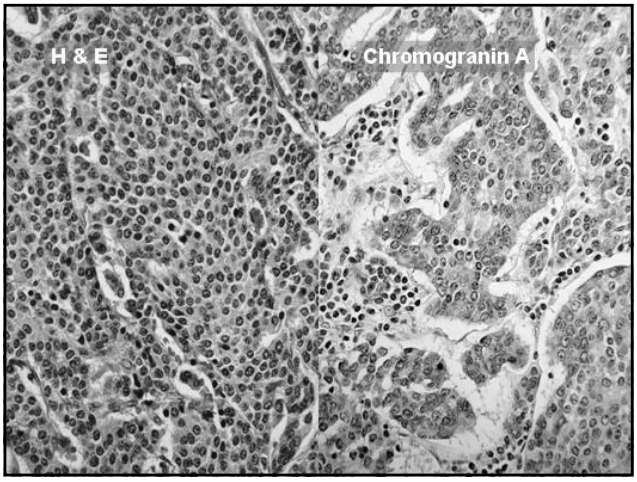
THE A, B,C's

Carcinoid tumours: origin

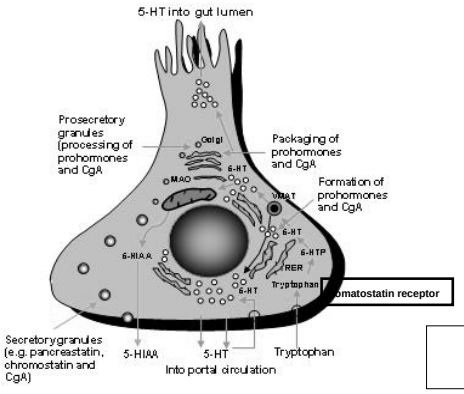


Definitions

- **Neuroendocrine: High Grade or <u>Low grade</u>**
- **Carcinoid is low grade: WDNT**
- **In Pancreas : Islet cell carinoma**
- **In Lung: Further divided**
  - **Typical – few mitoses, no necrosis**
  - **Aytpical – 2 mitoses per 10 HPF**



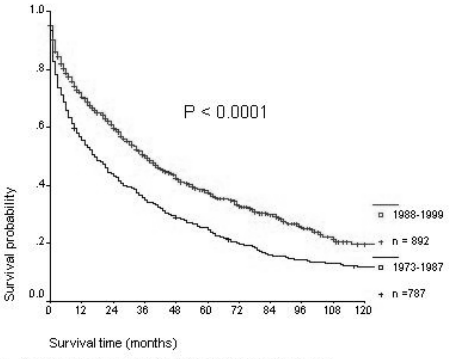
The neuroendocrine cell



Definitions

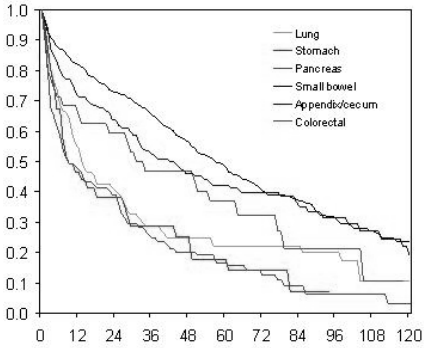
- **Serotonin: Biological peptide**
- **Somatostatin: Protein which binds to somatostatin receptor to regulate the amines and peptides secreted**
- **Octreotide is a synthetic somatostatin analog (SSA)**
- **Trade name is Sandostatin and Sandostatin LAR**

SEER 9: Metastatic Carcinoid



Talamonti M, Stuart K, Yao JC. *ASCO Education Book*. 2004; 206-218.

Metastatic Carcinoid: Survival by primary site



Molecular biology to clinical features

Primary site (Pt with met dz)	Median survival (months)	Described molecular abnormalities
Lung	13.1	Chr 11q, 3p loss
Stomach	8.7	Chr 11q, 18, X loss
Pancreas	31.0	Chr 11q deletion, karyotypic instability, MEN1
Small bowel	56.7	Chr 18 loss, 16q loss
Appendix/cecum	42.0	Chr 18 loss, 16q loss
Colon/rectum	8.6	NRP-2 loss

Outline

- **1. Presentation**
- **2. Diagnostic Work up and Follow**
- **3. Role of Surgery/ RFA/ Cryro**
- **4. Role of Peptide Receptor Radionuclide Therapy**
- **5. Role of Biologics and Somatostatin Analogs**
- **6. Role of Systemic Therapy**
  - **Chemotherapy and Novel drugs**

Outline

- **1. Presentation**

Presentation

- **Many discovered incidentally**
- **Symptoms due to:**
  - **Local tumour mass**
  - **Tumor-engendered fibrosis**
  - **Carcinoid Syndrome:**
    - **Secretion of biologically active amines and peptides**
    - **Carcinoid crisis**
    - **Carcinoid heart disease**

Hormonal Syndromes

Disease	Hormone/ peptide	Syndrome	Management
Carcinoid	Serotonin, 5HIAA, CgA, …	Flushing, diarrhea, asthma, valvular disease	Octreotide
Insulinoma	Insulin, C-peptide, proinsulin	Hypoglycemia	Diet, diazoxide, ?octreotide, steroid, glucagon drip
Glucagonoma	Glucagon	DM, migratory necrolytic erythema, thrombosis	Octreotide, ?perioperative anticoagulation, zinc
VIPoma	VIP	WDHA (watery diarrhea, hypokalemia, achlorhydria)	Octreotide
Gastrinoma	Gastrin	Diarrhea, peptic ulcer, reflux	PPI, octreotide

Carcinoid Crisis

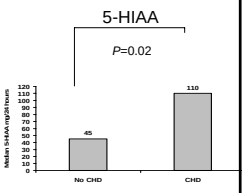
- **Life-threatening**
- **Spontaneously or precipitated by anesthesia, chemotherapy, infection or embolization procedures**
- **Severe flushing, diarrhea, hypo/hyper tension, tachycardia**
- **Immediate therapy iv octreotide**
- **Close monitoring before, during, and after surgical treatment**

Carcinoid Heart Disease

- **40% metastatic carcinoid tumors usually with liver metastases**
- **Pathology:**
  - **Thickening of right heart valves: fibrotic plaques**
  - **Valve insufficiency, RHF**

Carcinoid Heart Disease: Mechanisms

- **Serotonin plays important role**
  - **Serotonin receptors subtype 1B present in subendocardial cells**
  - **Significant correlation between carcinoid heart disease and urinary 5-HIAA**

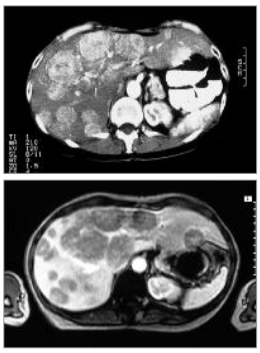


- **1. Presentation**
- **2. Diagnostic Work up and Follow**

Work Up

- **Biopsy**
- **Pathology: Ki 67 < or > 10 %**
- **CT/ MRI/ Ultrasound**
- **Octreotide and MIBG Nuclear Scans**
- **24 hour urine 5HIAA**
- **Serum Chromogranin A**
- **PET (Europe)**

Diagnosis: CT/MRI

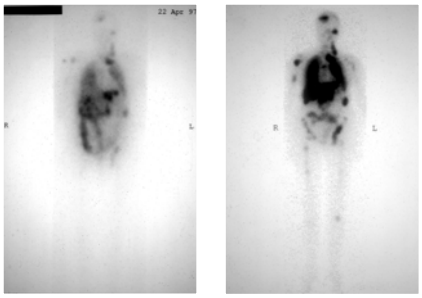


Contrast-enhanced CT scan (top) and MRI (bottom) of patient with metastatic small bowel carcinoid

Nuclear Peptide Scans

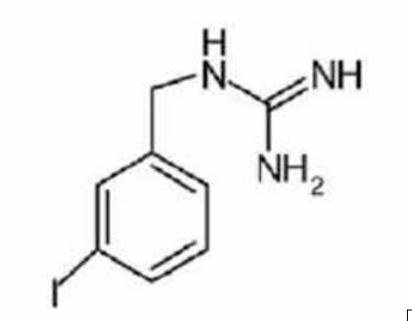
- **Both MIBG and somatostatin receptors are on carcinoid tumors and overexpressed**
- **Diagnostic Studies**
- **Indium 131 or I123 MIBG: sens 50%**
- **Indium 111 Octreotide sens 80%**

Diagnosis: OctreoScan



Anterior Posterior

MIBG



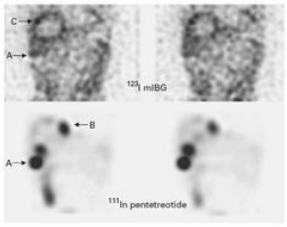


Fig. 4. Different lesions. Lesion B seen only on ^{111}In pentetreotide. Lesion C only seen on ^{123}I mIBG. Lesion A seen with both tracers.

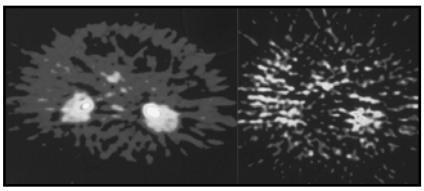
Diagnosis: Biochemical markers

- **5-HIAA Urine**
  - **Normal 3–15 mg/24 h urine**
  - **Baseline and 3- to 4-month in first year**
  - **Repeat if:**
    - **Disease progression is found**
    - **Change in therapy is being considered**
- **CgA Serum**
  - **Measure every 3 months in first year, then as per disease progresses**

PET

- FDG-PET helpful in localizing high grade neuroendocrine but not low grade
- 18F-DOPA PET better but less available
- Swiss : 11C-5HTP (5-hydroxytryptophan) for PET 5HTP precursor in seritonin
- 90% localized but 20 min half life

PET with 11C-5-hydroxytryptophan showing insulinoma in head of pancreas



- 1. Presentation
- 2. Diagnostic Work up and Follow
- 3. Role of Surgery

Definition of the Problem

- 75% will develop liver metastases
- 80% with liver mets will die < 5 years
- Progressive liver mets leading cause of mortality (replaced hormone excess)
- Surgery :
  - Local tumor obstruction, bleeding, perforation
  - Symptoms from fibrosis

Controversial

- **Role of extended, radical or en bloc resection of the primary tumor**
- **Role of metastatic resections?**
  - **Morbitity and mortality?**
  - **Symptom control?**
  - **Survival benefit**

Aggressive Resections

- **Norton et al. 2003: 20 patients with advanced WDET**
  - **15/20 (75%) underwent complete resections**
  - **Pancreaticoduodencectomy –8**
  - **Superior mesenteric vein resection/reconstruction – 3**
  - **Splenectomy – 11**
  - **Nephrectomy – 2**
  - **Liver resections – 6**
- **Morbidity = 30%**
- **Mortality = 0**
- **Actuarial 5 yr-survival = 80%**
- **Disease free-survival: all recurred by 7 years**

Author/Institution	Year	Patients	Operative Mortality(%)
Que/Mayo	1995	74	3
Doussett/Paris	1996	17	6
Chen/Hopkins	1998	15	0
Chamberlain/MSKCC	1999	34	6
Yao/Northwestern	2001	16	0
Elias/Institut Gustave	2002	47	5
Sarmiento/Mayo	2003	170	1.2

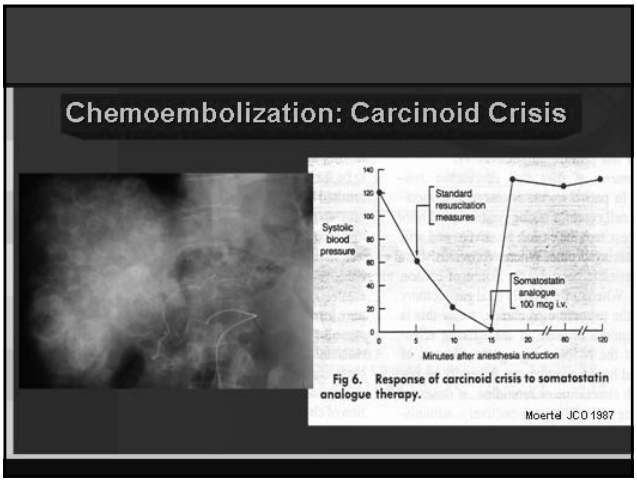
Author/Institution	Year	Patients	Sympton Control(%)
Que/Mayo	1995	74	90
Doussett/Paris	1996	17	88
Chen/Hopkins	1998	15	---
Chamberlain/MSKCC	1999	34	90
Yao/Northwestern	2001	16	71
Elias/Institut Gustave	2002	47	---
Sarmiento/Mayo	2003	170	96

Author/Institution	Year	Patients	Survival(%)
Que/Mayo	1995	74	73% at 4y
Doussett/Paris	1996	17	46% a t4y
Chen/Hopkins	1998	15	73% at 5y
Chamnberlain/MSKCC	1999	34	76% at 5y
Yao/Northwestern	2001	16	70% at 5y
Elias/Institut Gustave	2002	47	71% at 5y
Sarmiento/Mayo	2003	170	61% at 5y

Author	Func/Non	Sync/Metac.	#Mets	%Liver	Comp/Inc
Que	no	no	no	-	no
Doussett	no	no	no	no	yes
Chen	no	-	-	-	-
Chamerlain	no	no	no	no	yes
Yao	no	yes	yes	no	-
Elias	-	no	no	no	yes
Sarmiento	no	-	-	no	yes

Hepatic Artery Embolization

		RR	Dur
Moertel et al, 1994	n=111		
Embolization		60%	4 mo
Chemoembolization (Doxo, DTIC, STZ, 5FU)		80%	18 mo
Eriksson B et al, 1998	n=29		
Embolization		38%	7 mo
Kim YH et al, 1999	n=30		
Chemoembolization		37%	24 mo
Diamandidou et al, 1998	n=20	78%	
Chemoembolization			



Radiofrequency Ablation: Results

Percutaneous: 43 neuroendocrine metastases in 21 pts
- 2 complications
- 5% recurrence at 6 months
- 4/15 had no residual tumor
  - » Hellman et al. World J Surg 2002;26:1052-6

- Laparoscopic RF: 34 neuroendocrine metastases
  - 80% had decreased symptoms
  - 65% decreased hormonal/tumor markers
  - 28% developed new lesions
  - 41% stable disease
    - » Berber et al World J Surg 2002;26:985-90

Liver transplantation in malignant neuroendocrine tumors

(Lehnert T. Transplantation 1998;66:1307)

Total no. of patients	**103**
EPT	**48**
Carcinoids	**43**
2-year survival	**60%**
5-year survival	**47%**
Recurrent free survival	**24%**

Surgical Conclusions

- **Aggressive resections can be done, acceptable morbidity and mortality**
- **Improved symptom control and extended survival likely**
- **Patients to benefit the most are those rendered disease free**
- **Precise patient selection and disease extent**
- **Ultimate disease recurrent and progression likely**
- **An initial period of medical therapy is often recommended to allow time for observation and make surgery or ablation safer**

Outline

- **1. Presentation**
- **2. Diagnostic Work up and Follow**
- **3. Role of Surgery**
- **4. Role of Peptide Receptor Radionuclide Therapy**

Nuclear Peptide Targeted Therapy

- **Diagnostic I131 MIBG: If positive: potential treat with high dose 131-iodine-MIBG**
- **I111 Octreotide: If positive: potential treat with high dose**
  - **111 Indium-octreotide**
  - **90 Yttrruim-octreotide**
  - **177 Lutetium-octreotide**
- **RR 10-40% Survival Benefit?**
- **Considered Investigational**

Tumor targeted irradiation in neuroendocrine tumors

^{111}Ind-DTPA-octreotide		**n=38**	***(Krenning et al, 1999)***
Total dose 20 Gbq			
	Radiological response	**30%**	
	Disease stabilization	**40%**	
^{90}Y-DOTATOC		**n=22**	***(Valkemaa et al, 2000)***
Phase I	**Radiological response**	**10%**	
	Disease stabilization	**45%**	
^{90}Y-DOTATOC (6000 MBq/d)		**n=41**	***(Waldherr et al, 2001)***
	CR+PR	**24%**	
	MR+SD	**61%**	

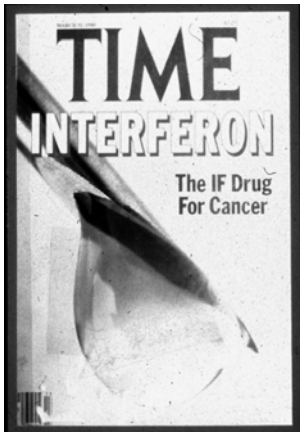
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy in GEP Tumors: AntiTumor Effects 3 months follow-up

Progressive at baseline	PR/CR/MR	SD	PD	Total
Yes	55 47%	30 26%	32 27%	117
No	30 40%	33 45%	11 15%	74
Unknown	40 44%	37 41%	14 15%	91
Total	125 44%	100 36%	57 20%	282

Erasmus MC

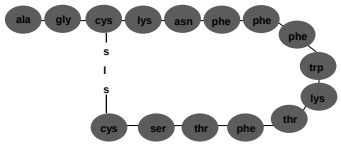
Outline

- **1. Presentation**
- **2. Diagnostic Work up and Follow**
- **3. Role of Surgery**
- **4. Role of Peptide Receptor Radionuclide Therapy**
- **5. Role of Biologics and Sandostatin Analogs (SSA)**

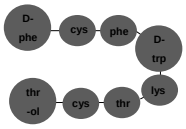


Biologics: Interferon

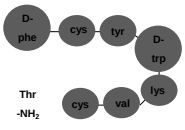
- **Biochemical response in 40%**
- **Tumor response seen in <10%**
- **Side effects: fever, fatigue, anorexia, weight loss, alopecia, myelosuppression, liver dysfunction, clinical depression**
- **Used in Europe not North America**



Human somatostatin



Octreotide acetate



lanreotide

Somatostatin Analogs: SSA

- Somatostatin analogs bind to somatostatin receptors
- Biochemical responses > 70%
- Objective response < 5 %
- No survival benefit ? Cytostatic
- ? Super high doses

Sandostatin BCCA 2007

- Symptomatic, 5HIAA high: Approved
- Symptomatic, 5HIAA low: Approved
- No symptomatic, 5HIAA high: Approved
  - Goal: prevent carcinoid heart
- No symptomatic, 5HIAA low: Not Approved
  - Goal: Improve survival
  - Controversial not proven

Somatostatin Analogs

- Start with Octreotide 100 ug sc tid for 4 weeks
- At two weeks over lap with Sandostatin LAR at 20 mg q 4 weeks
- Increase at 10 mg increments q3-4 weeks if symptoms not improving or 5 HIAA not dropping

Outline

- 1. Presentation
- 2. Diagnostic Work up and Follow
- 3. Role of Surgery
- 4. Role of Biologics and Sandostatin
- 5. Systemic Treatment
  - Chemotherapy and Novel Therapy

Cytotoxic therapy in carcinoids

Drug	Dose, regimen	Pts	OR(%)	Median duration (mo)
Single agents:				
Doxorubicin (DOX)	60 mg/m^2 q 3-4 w	81	21	6
5-FU	500 m/m^2/d x 5 d q 5 w	30	17-26	3
Streptozotocin (STZ)	500-1500 mg/m^2/d x 5 d q 3-5 w	14	0-17	2
Dacarbacine (DTIC)	250 mg/ m^2/d x 5 d q 4-5 w	15	13	4.5
Cisplatin	45-90 mg/ m^2/ q 3-4 w16	6	4.5	
Combinations:				
Streptozotocin + 5-FU	STZ 500 mg/ m^2/d x 5 q 3-6 w 5-FU 400 mg/ m^2/d x 5 q 3-6 w	175	7-33	3-7
Streptozotocin + Doxorubicin	STZ 1000 mg/ m^2/w for 4 w DOX 25 mg/ m^2/w then q 2 w	10	40	5
Streptozotocin + Cyclophosphamide (CTX)	STZ 500 mg/m^2/d q 6 w CTX 100 mg/ m^2 once q 3 w	24	39	6.5
Etoposide + Cisplatin	Etop 130 mg/ m^2/d x 3 d Cispl 45 mg/ m^2/d d 2 and 3 cycle q 4 w	13	0	-

Carcinoid: Chemotherapy

- Chemotherapy
  - E1281 (JCO 2005)
  - 5FU/doxorubicin
    - PFS = 4.5 months, OS = 15.7 months
  - 5FU/streptozocin
    - PFS = 5.3 months, OS = 24.3 months

BCCA

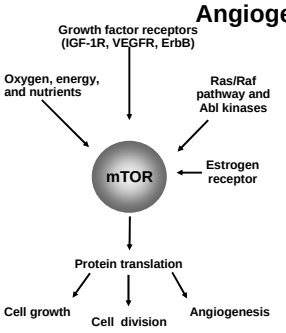
- **ENDO 1:**
  - **Streptozotocin/ Adriamycin**
  - **Streptozotocin/ 5 FU**
- **ENDO 2:**
  - **Carmustine/ 5 FU**

New Drugs

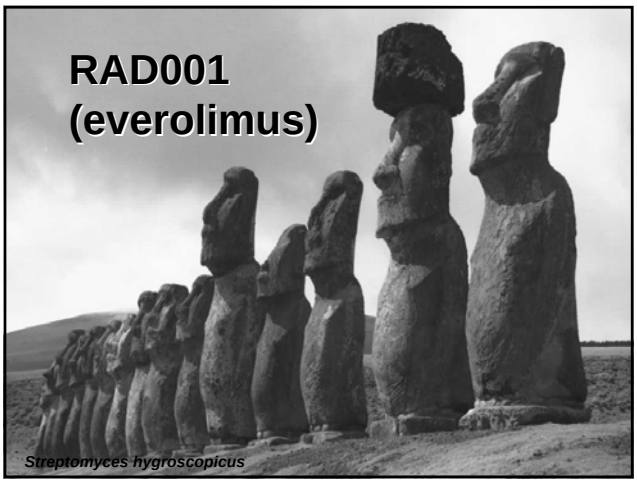
mTOR

mTOR (mammalian target of rapamycin) is an intracellular protein (enzyme) that acts as a central regulator for cell growth, transcription, proliferation, and angiogenesis in cancer

mTOR
Controls Cell Growth, Proliferation and Angiogenesis



- mTOR is a kinase in the PI3-K/Akt signaling pathway
- Integrates multiple signals
  - Growth factor receptor activity
  - Cellular energy, nutrients, and oxygen levels
  - Signals from other cellular signaling pathways
  - Estrogen receptor signaling
- Controls production of proteins regulating cell growth, cell division, and angiogenesis in response to these signals



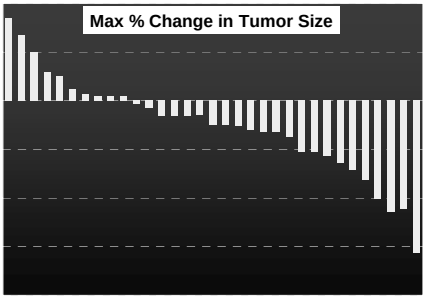
RAD001
Single Agent Activity in NET
ASCO 2006: Dr J. Yao, MD Anderson (IIT)

17 patients with disease progression at study entry

- **3 PR, 10 SD, 4 PD with RAD001 5 mg/d (10 mg/d ongoing)**
- **11 (65%) progression-free at 6 mos**

Phase II RADIANT 1Study in Advanced Pancreatic Islet Cell after Chemotherapy Failure, started in 2006
Ph III in 2007, post-interim analysis of RADIANT 1

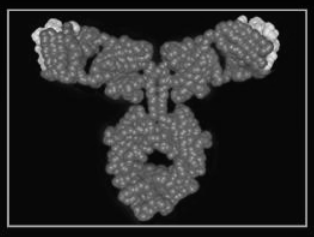
Phase II Trial in Neuroendocrine Tumors: Individual Patient Data (Yao ASCO 2006)



70% of pts have tumor shrinkage (of first 33 pts)
Stable disease, minor and partial responses are generally durable

Increased VEGF expression is associated with poor prognosis in neuroendocrine tumors

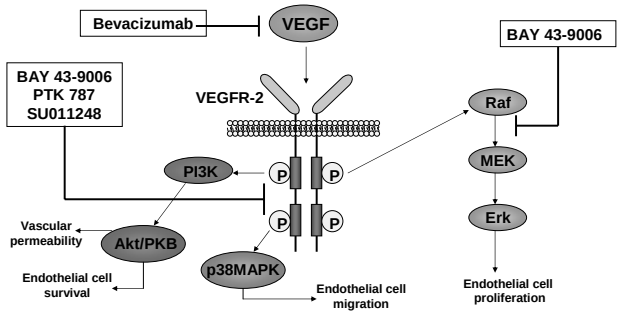
Bevacizumab (BV; rhuMAb VEGF)



- Recombinant humanized anti-VEGF MAb
- Binds and neutralizes all forms of VEGF A
- $T_{1/2}$ 17-21 days

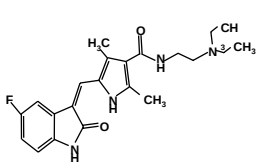
Avastin™ (bevacizumab) [package insert]. San Francisco, Calif: Genentech, Inc; 2004.

Inhibiting VEGF



Rini JCO 2005

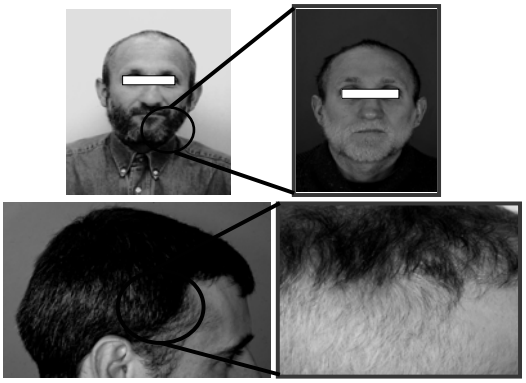
SU011248 - Sunitinib



- Small molecule TKI
- 50mg daily 4 weeks on – 2 weeks off
- Good oral bioavailability, unaffected by food
- Metabolized in liver via CYP4503A4 ($t_{1/2}$ 40hr, metabolite 80 hr)
- Potential CYP4503A4 interactions
- Active metabolite SU012662
- Linear PK within tested doses (25-150mg)
- ATP site–directed competitive inhibitor
  - Directly binds to kinase domain to prevent phosphorylation and activation of substrates

Sun L, et al. *J Med Chem.* 2003;46:1116-1119.

Hair color changes with Sutent



Slide Courtesy of Dr. Escudier

Other VEGF Inhibitors

- Other targeted agents in trial or about to start trials in neuroendocrine tumors
  - SU011248
  - PTK/ZK
  - BAY 43-9006
  - GW786034

Conclusion: Neuroendocrine Tumors

THE A, B,C's

Conclusion

- **Mutlimodality approach: Surgery, Medical Oncology, Nuclear medicine, radiology**
- **Somatostatin Analogs has resulted in significant advances in the management of neuroendocrine tumors**
- **Therapeutic nuclear treatments evolving and encouraging**
- **Future lies in new drugs**