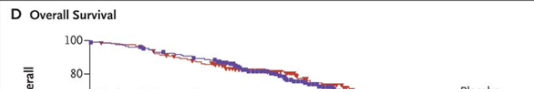
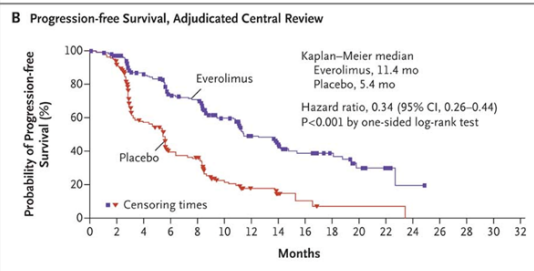
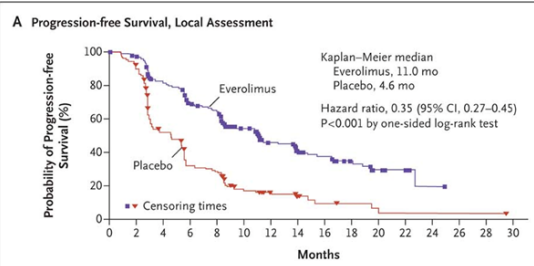
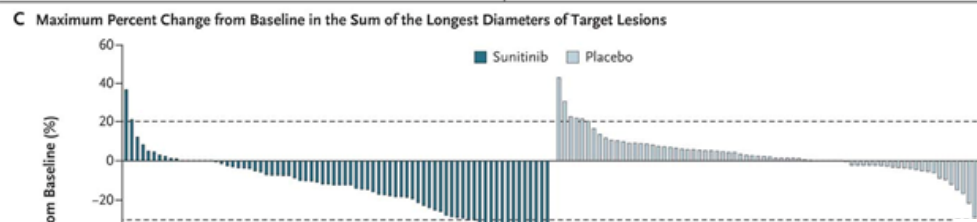
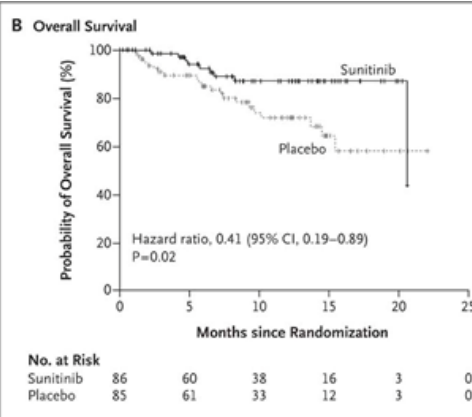
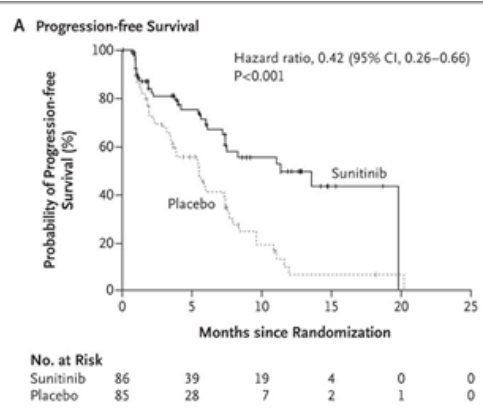


Clinical case 1: Pancreatic neuroendocrine tumour

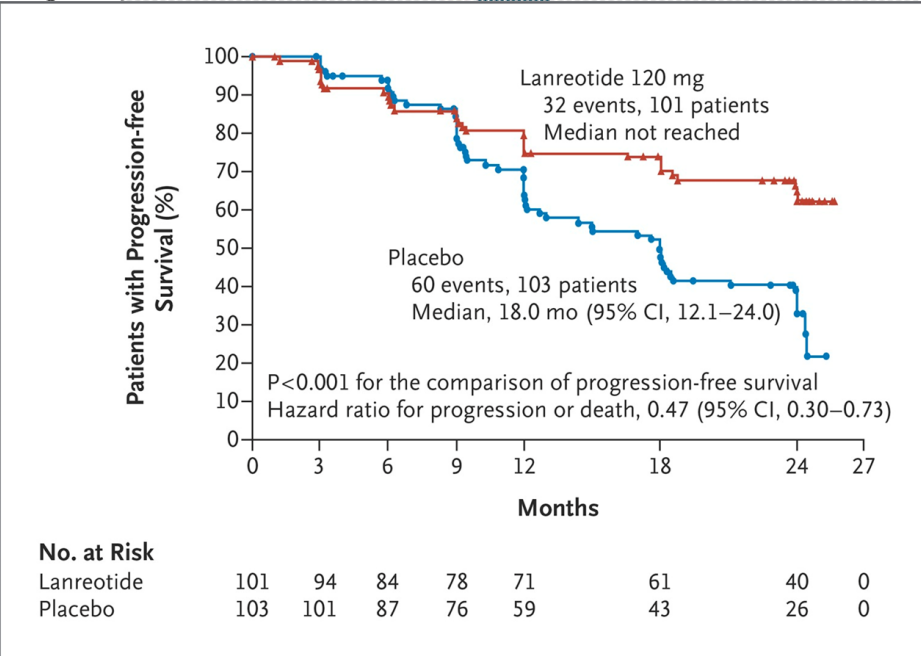
How to manage the possibilities of systemic treatment

Jorge Barriuso
University of Manchester



C Progression-free Survival in Subgroups

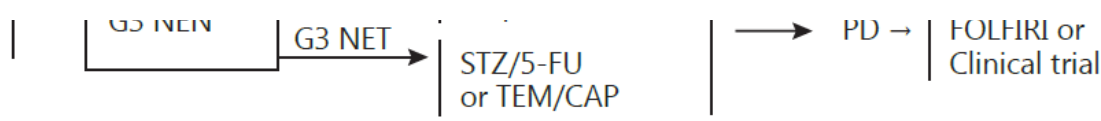
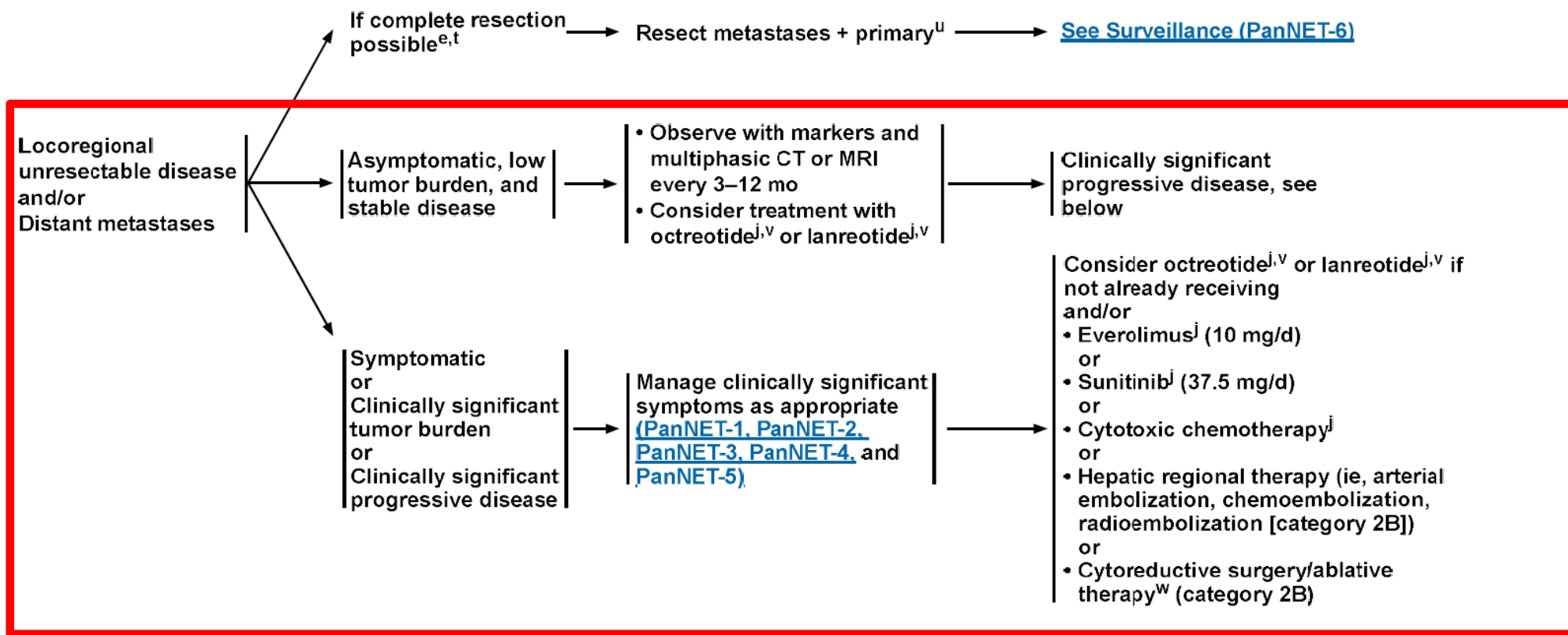
Subgroups	No.	Hazard Ratio (95% CI)	P Value
Local investigator review	410	0.35 (0.27-0.45)	<0.001
Central adjudicated review	410	0.34 (0.26-0.44)	<0.001
Previous chemotherapy			
Yes	189	0.34 (0.24-0.49)	<0.001
No	221	0.41 (0.29-0.58)	<0.001
WHO performance status			
0	279	0.39 (0.28-0.53)	<0.001
1 or 2	131	0.30 (0.20-0.47)	<0.001
Age			
≤65 yr	299	0.39 (0.29-0.53)	<0.001
>65 yr	111	0.36 (0.22-0.58)	<0.001
Sex			
Male	227	0.41 (0.30-0.58)	<0.001
Female	183	0.33 (0.23-0.48)	<0.001
Race			
White	322	0.41 (0.31-0.53)	<0.001
Asian	74	0.29 (0.15-0.56)	<0.001
Region			
America	185	0.36 (0.25-0.52)	<0.001
Europe	156	0.47 (0.32-0.69)	<0.001
Asia	69	0.29 (0.14-0.56)	<0.001
Previous long-acting SSA			
Yes	203	0.40 (0.28-0.57)	<0.001
No	207	0.36 (0.25-0.51)	<0.001
Tumor grade			
Well differentiated	341	0.41 (0.31-0.53)	<0.001
Moderately differentiated	65	0.21 (0.11-0.42)	<0.001

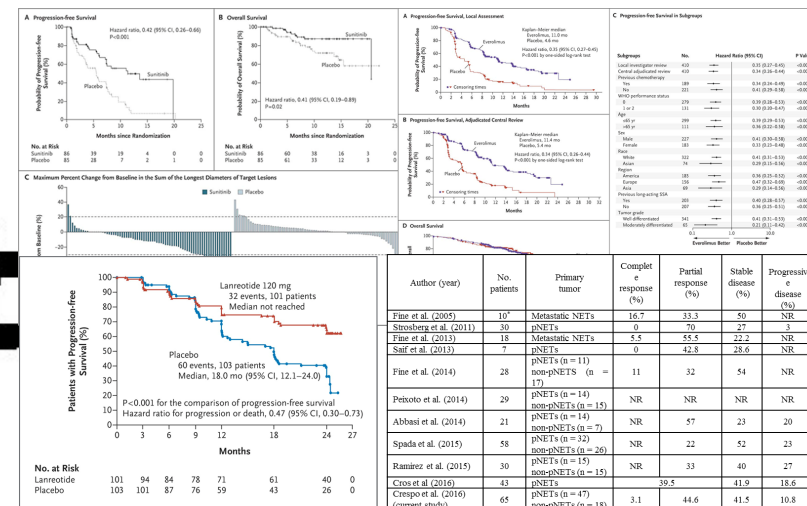
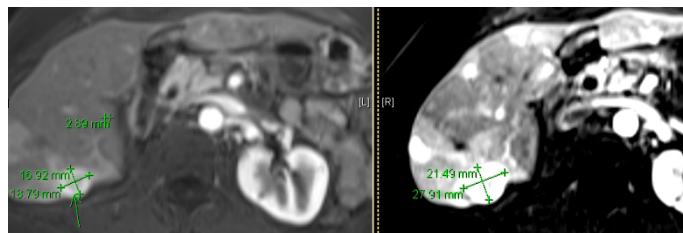


Author (year)	No. patients	Primary tumor	Complete response (%)	Partial response (%)	Stable disease (%)	Progressive disease (%)
Fine et al. (2005)	10*	Metastatic NETs	16.7	33.3	50	NR
Strosberg et al. (2011)	30	pNETs	0	70	27	3
Fine et al. (2013)	18	Metastatic NETs	5.5	55.5	22.2	NR
Saif et al. (2013)	7	pNETs	0	42.8	28.6	NR
Fine et al. (2014)	28	pNETs (n = 11) non-pNETs (n = 17)	11	32	54	NR
Peixoto et al. (2014)	29	pNETs (n = 14) non-pNETs (n = 15)	NR	NR	NR	NR
Abbasi et al. (2014)	21	pNETs (n = 14) non-pNETs (n = 7)	NR	57	23	20
Spada et al. (2015)	58	pNETs (n = 32) non-pNETs (n = 26)	NR	22	52	23
Ramirez et al. (2015)	30	pNETs (n = 15) non-pNETs (n = 15)	NR	33	40	27
Cros et al (2016)	43	pNETs		39.5	41.9	18.6
Crespo et al. (2016) (current study)	65	pNETs (n = 47) non-pNETs (n = 18)	3.1	44.6	41.5	10.8

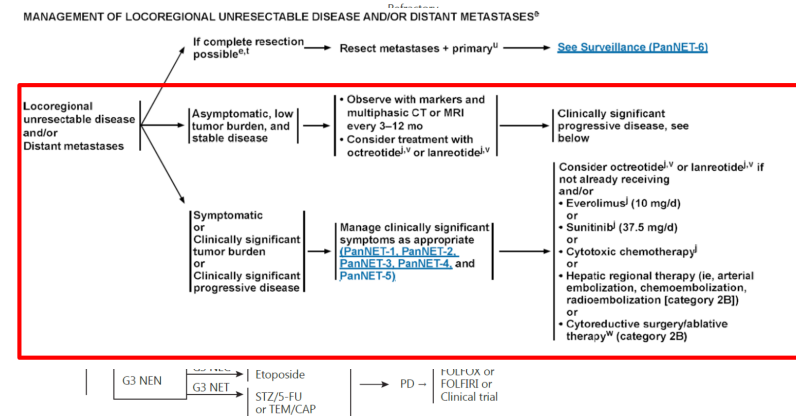
MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES^e

Refractory syndrome
Diazoxide (insulinoma) → Consider debulking surgery of LM (see fig. 1)





Name	Gene	NET manifestation	Other manifestation
MEN1	MEN1	Parathyroid (>90%), gastroenteropancreatic (50%), anterior pituitary (30%), lung and thymus (10%)	Adrenocortical tumors
MEN2A (FMTC)	RET	Medullary thyroid (90-100%), adrenal medulla (20-80%), parathyroid (20%) ^a	Marfanoid habitus
MEN2B	RET	Parathyroid, medullary thyroid (100%), adrenal medulla (50%)	Neurofibroma, cafe-au-lait spots
MEN4	CDKN1B	Parathyroid, pancreas, pituitary	
Neurofibromatosis type 1	NF1	Adrenal medulla (1-5%), duodenum	
von Hippel-Lindau	VHL	Adrenal medulla and sympathetic ganglia (15%), pancreas (10%)	Hemangioblastoma, renal carcinoma
Familial PGL 1-5	SDHA-D, SDHAF2	Sympathetic and parasympathetic paraganglia, Adrenal medulla	GIST, renal carcinoma
Familial PCC and PGL syndromes	TMEM127, MAX, FH, MDH2	Adrenal medulla, sympathetic ganglia (TMEM127 30%)	
Polycytemia parangangioma syndrome	EPAS1	Sympathetic ganglia, adrenal medulla, duodenum	Polycytemia
Tuberous sclerosis complexes	TSC1, TSC2	Pancreas	Hamartoma
HPT-JT syndrome	HRPT2	Parathyroid adenoma (80%) and carcinoma (15%)	



First visit Jul 2006

- 43y woman
- PMH:
 - 1986 Diagnosed with Von Hippel Lindau at age 24. Retinal abnormalities managed with Laser treatment. Follow up by US yearly with urology team.
 - May 03 left nephron excision of renal carcinoma.
 - October 05 Cerebellar haemangioblastoma removed.
 - Jan 06 Routine US suggested possible right renal mass although CT scan suggested **locally invasive pancreatic mass** with 3 separate solid masses in the right kidney. MR confirmed bulky pancreatic body mass.
 - May 06 Underwent laparotomy with distal pancreatectomy and splenectomy and limited right upper pole nephrectomy. **The surgical team felt that there was residual tumour left on the anterior wall of the Aorta** at the end of the procedure.
- Post-operative bowel obstruction managed conservatively.

First visit

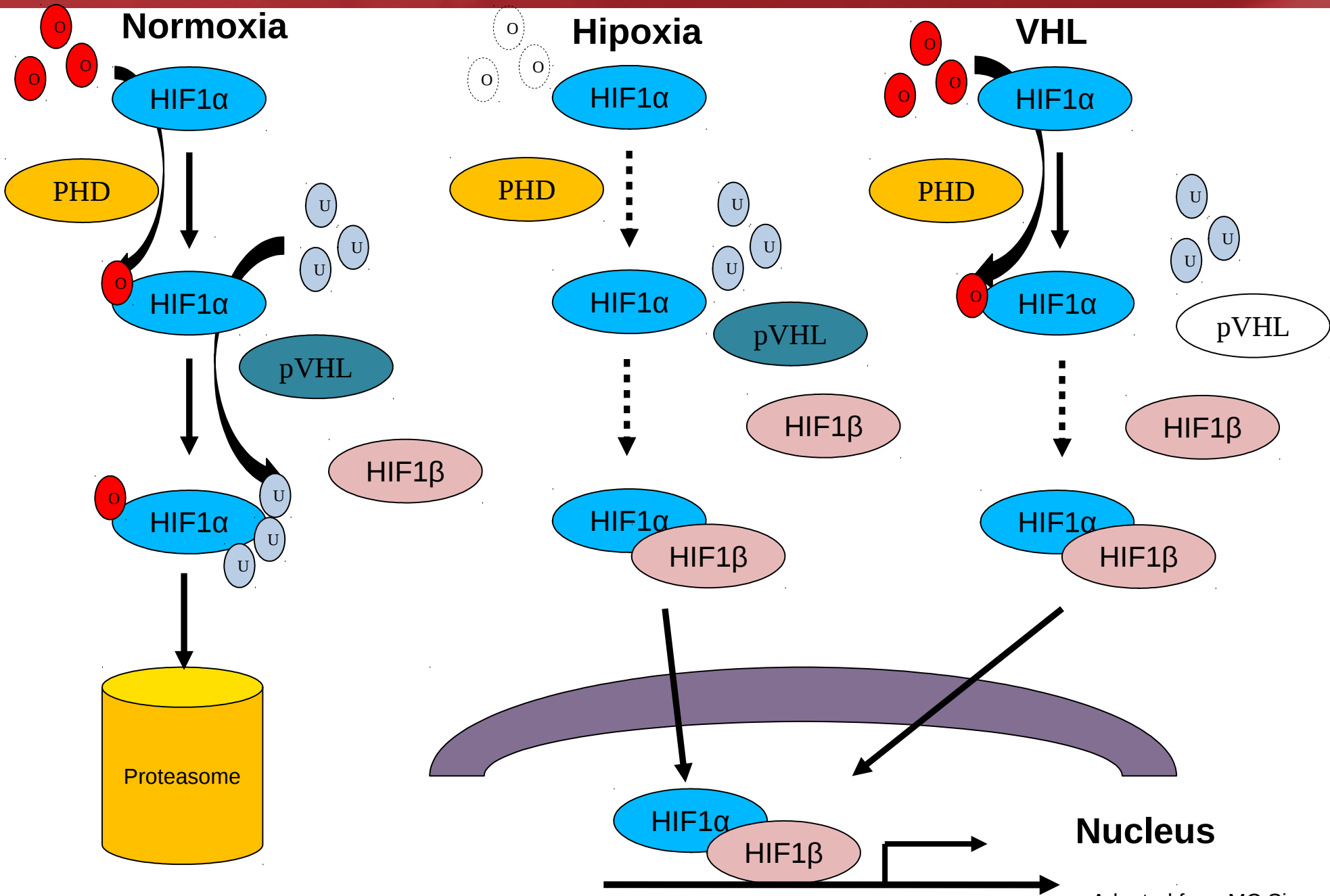
- Symptoms:
- Intermittent abdominal cramps
- Family History: Father had VHL with bilateral renal involvement, died at age 52. Two brothers one unaffected and another with VHL. He is near blind. He has 3 cerebellar cysts removed and surgery for kidneys. She has one son free of VHL.
- Social history: dermatology nurse.
- Ex-smoker

Impression:

Patient with VHL and R2 resection of a pancreatic neuroendocrine tumour.

Pathology: “Well differentiated pancreatic neuroendocrine carcinoma, low grade malignant, in view of lymph node involvement (WHO 200/2004) / NET, grade 1 (WHO 2010)” Ki67<2%, mitotic index 1/10hpf. Synaptophysin and Chromogranin positive. (Pathology review performed in March 2013)

Name	Gene	NET manifestation	Other manifestation
MEN1	<i>MEN1</i>	Parathyroid (>90%), gastroenteropancreatic (50%), anterior pituitary (30%), lung and thymus (10%)	Adrenocortical tumors
MEN2A (FMTC)	<i>RET</i>	Medullary thyroid (90–100%), adrenal medulla (20–80%), parathyroid (20%) a	
MEN2B	<i>RET</i>	Parathyroid, medullary thyroid (100%), adrenal medulla (50%)	Marfanoid habitus
MEN4	<i>CDKN1B</i>	Parathyroid, pancreas, pituitary	
Neurofibromatosis type 1	<i>NF1</i>	Adrenal medulla (1–5%), duodenum	Neurofibroma, cafe-au-lait spots
von Hippel–Lindau	<i>VHL</i>	Adrenal medulla and sympathetic ganglia (15%), pancreas (10%)	Hemangioblastoma, renal carcinoma
Familial PGL 1-5	<i>SDHA-D, SDHAF2</i>	Sympathetic and parasympathetic paraganglia, Adrenal medulla	GIST, renal carcinoma
Familial PCC and PGL syndromes	<i>TMEM127, MAX, FH, MDH2</i>	Adrenal medulla, sympathetic ganglia (<i>TMEM127</i> 30%)	
Polycytemia paraganglioma syndrome	<i>EPAS1</i>	Sympathetic ganglia, adrenal medulla, duodenum	Polycytemia
Tuberous sclerosis complexes	<i>TSC1, TSC2</i>	Pancreas	Hamartoma
HPT-JT syndrome	<i>HRPT2</i>	Parathyroid adenoma (80%) and carcinoma (15%)	



- Considered for local treatment of the residual disease:
 - Radiotherapy
 - MIBG
 - Radio-labelled octreotide

Nov 2006

- New renal lesion
- Patient concern about residual disease
- Signs of pancreatic insufficiency: weight loss and steatorrhea
- Plan: IFN 3MU X 3 days weekly

March 2007

- Anorexia, weight lose
- Depression that needs the introduction of mirtazapine



Sept 2007

- New nephron sparing operation
- Stopped IFN due to operation, patient feeling “better than ever”

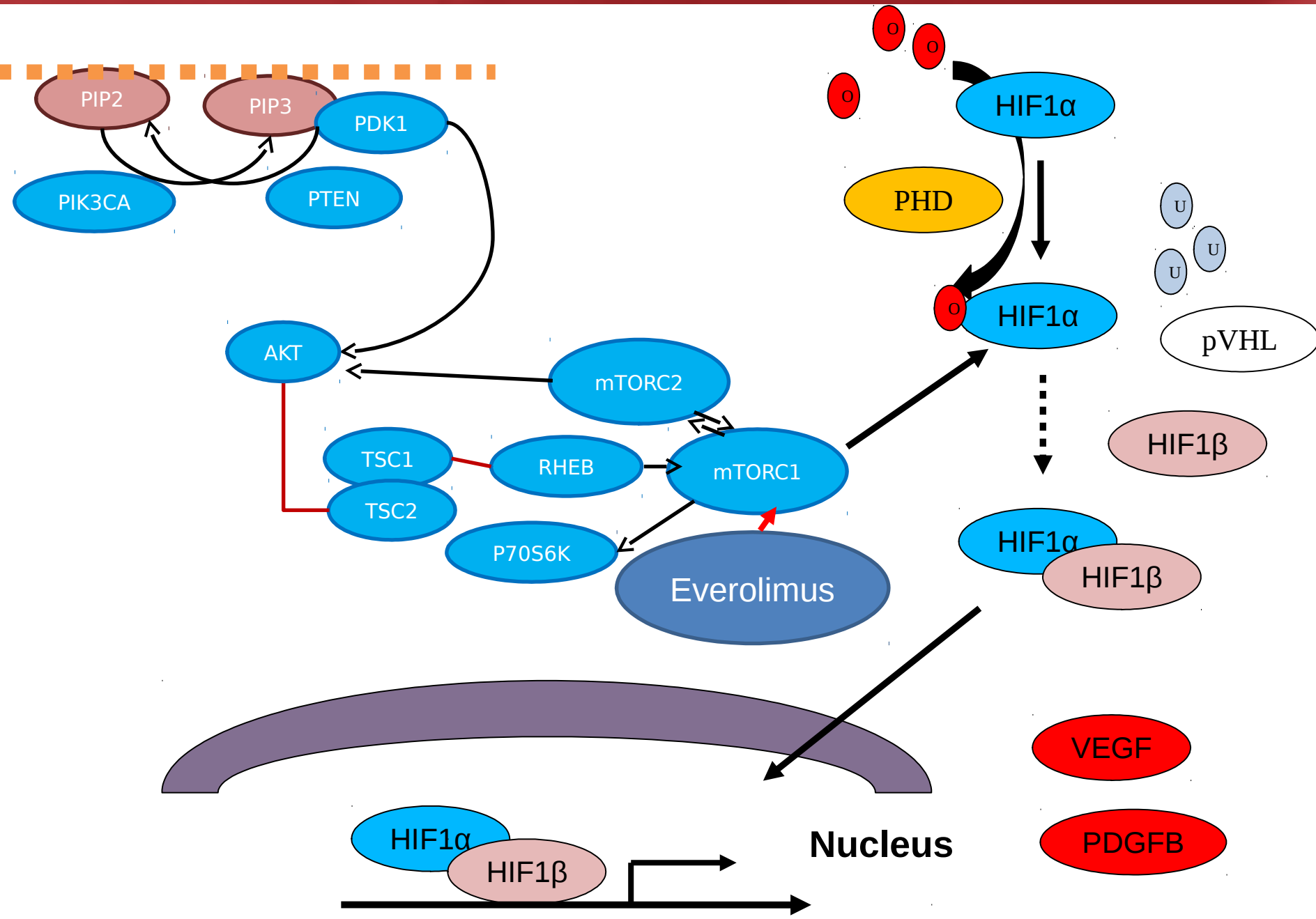
January 2008

- Stopped IFN due to intolerance

May 2012

- Commences on Everolimus 10 mg PO OD





May 2012

- Commences on Everolimus 10 mg PO OD
- Main toxicities: G1 mucositis, G1 fatigue, G2 diarrhoea
- October 2012, underwent a left salpingo-oophorectomy due to a Falopian abscess.

Table 3. Drug-Related Adverse Events Occurring in at Least 10% of Patients.

Adverse Event	Everolimus (N=204)		Placebo (N=203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
<i>no. of patients (%)</i>				
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

* Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

† All types of infections are included.

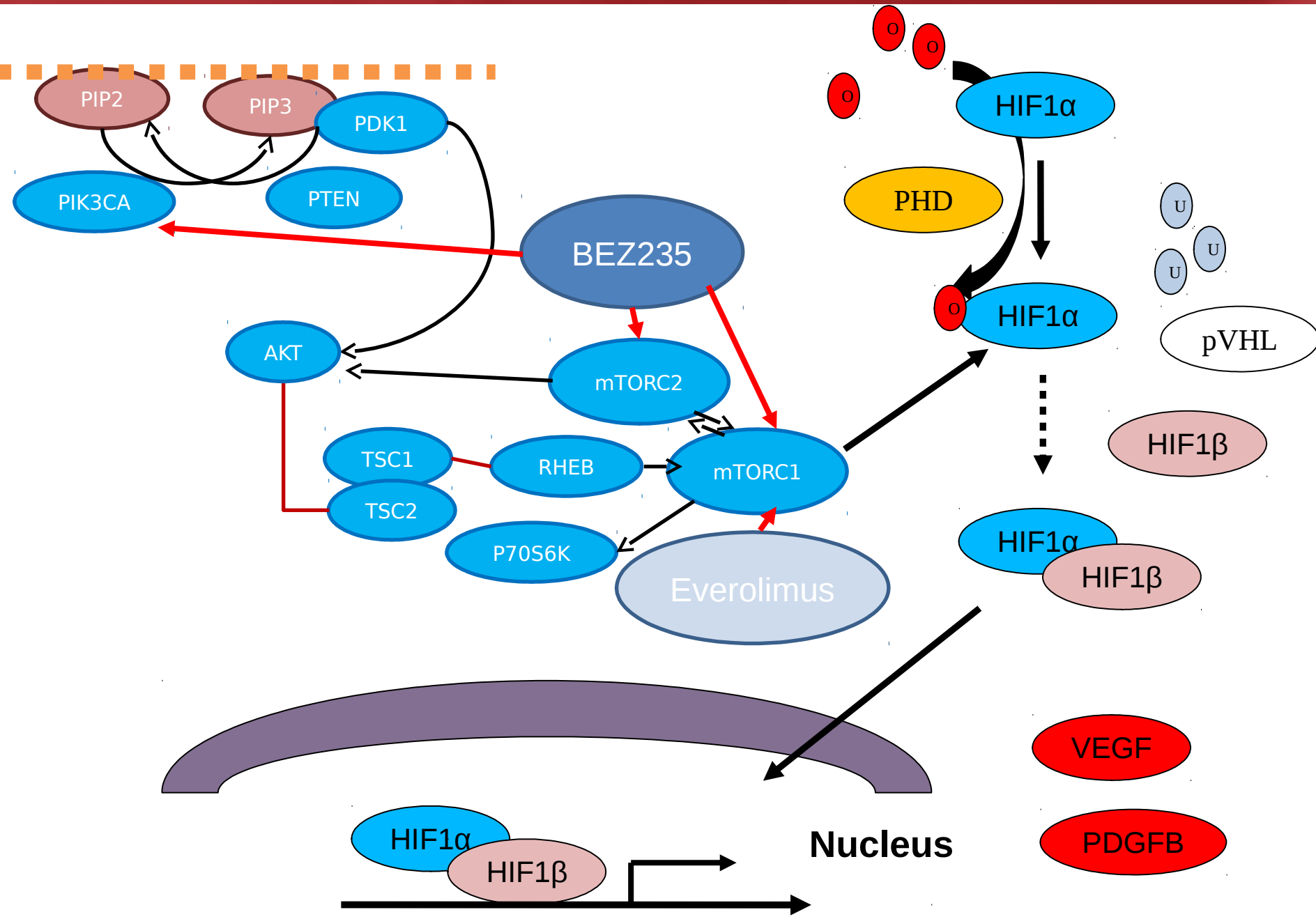
‡ Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

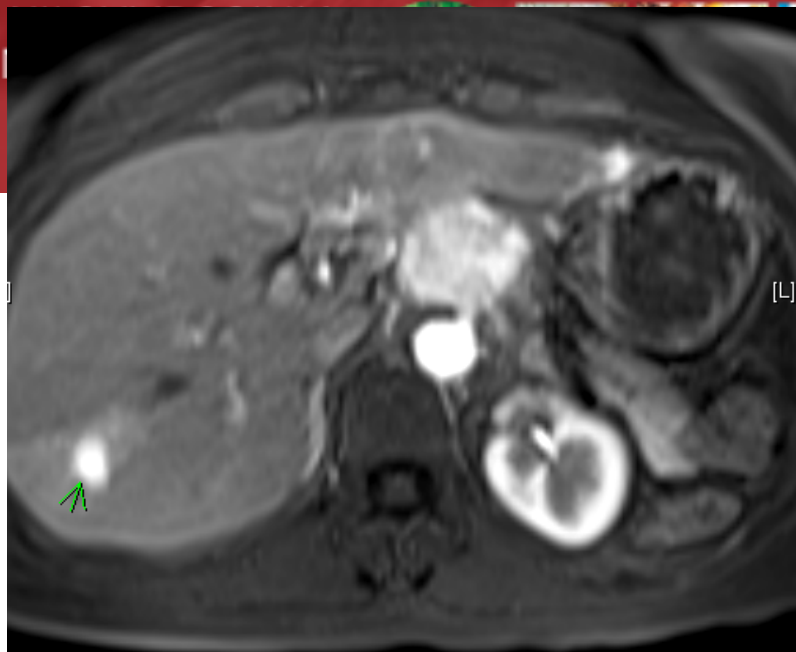
November 2012

- Resumes Everolimus at 5mg

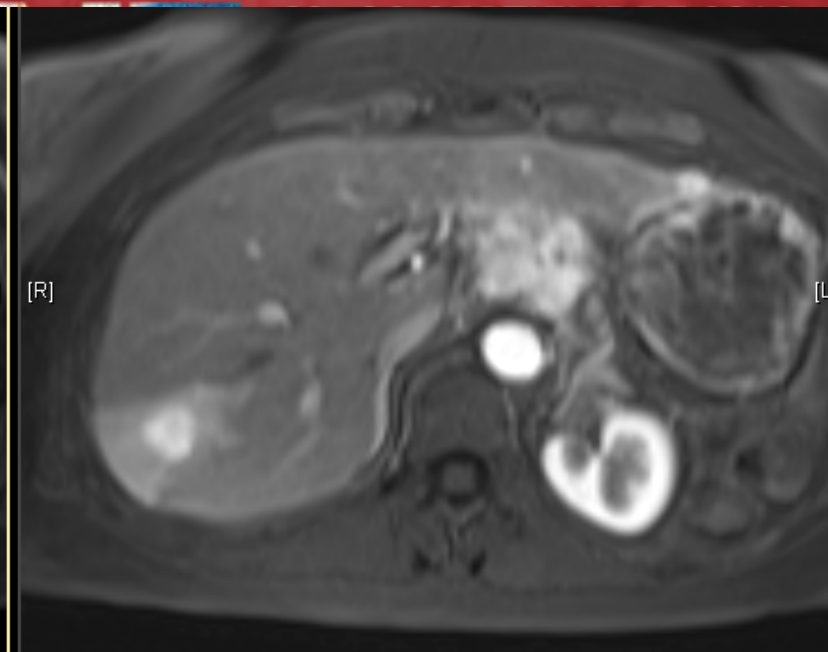
January 2013

- Confirmed progressive disease around the coeliac axis

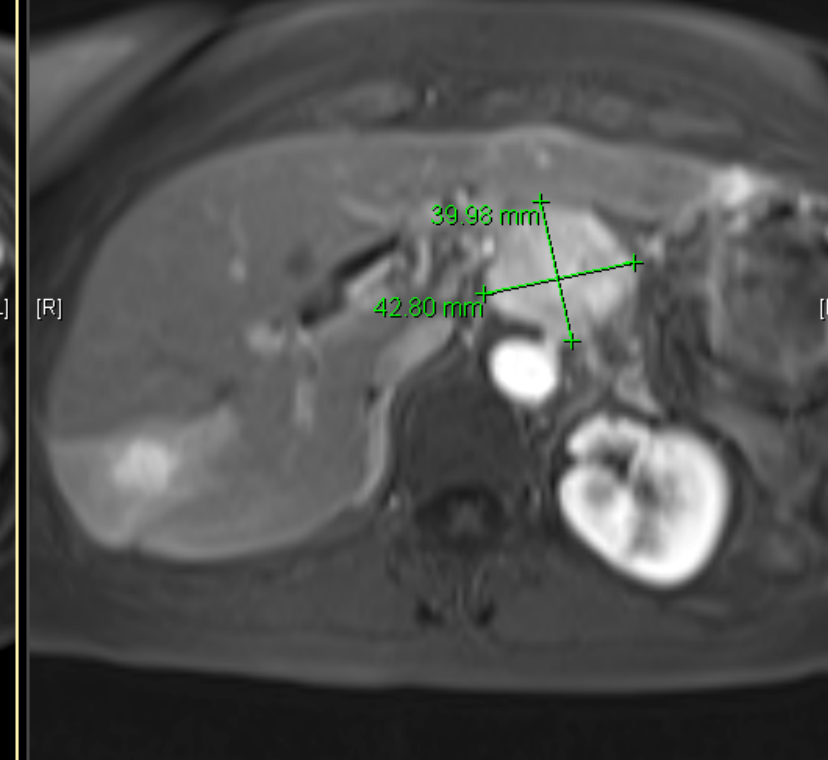
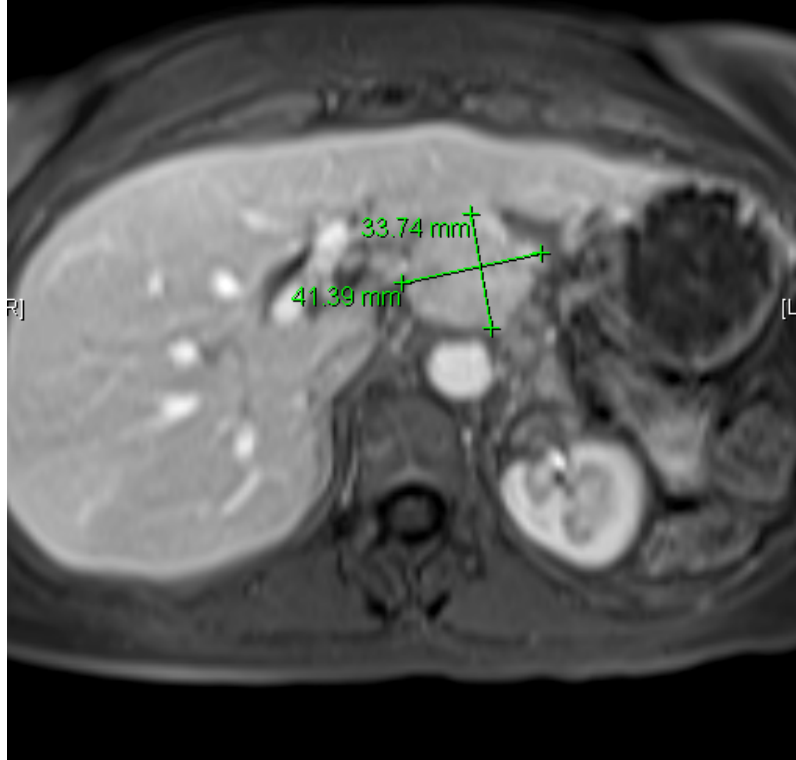




March 13



October 14



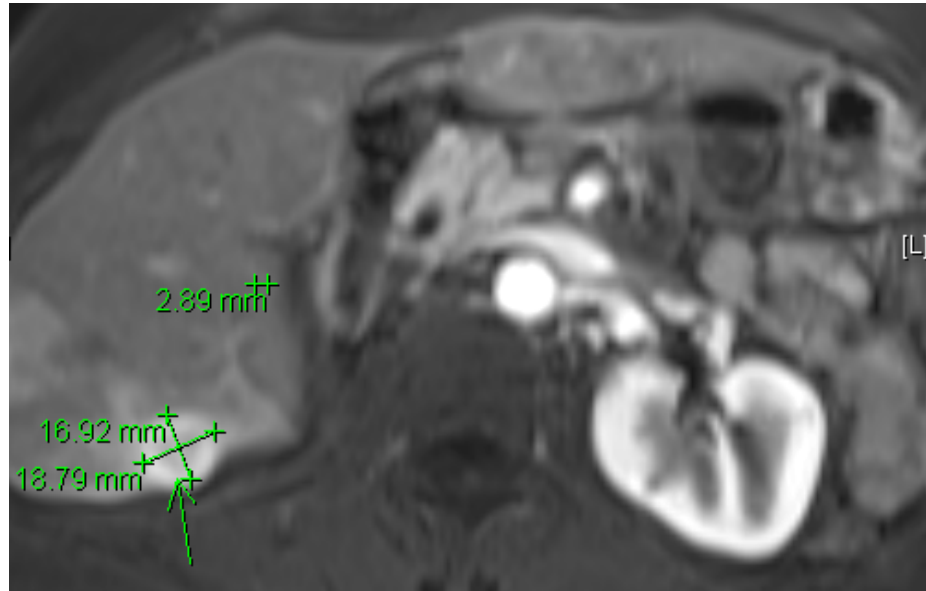
March 2013

- Considered for Phase II clinical trial of BEZ235 in everolimus resistant pNET patients.
- Dose 300 mg BD PO
- ECOG:1

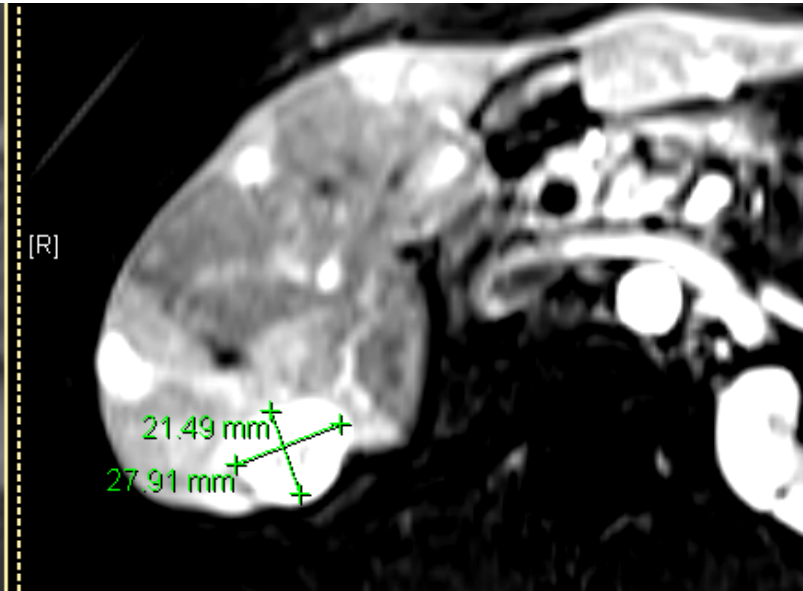
- Main toxicities:
 - G3 diarrhoea, needs dose reduction as per protocol (200mg BD PO)
 - G1 fatigue
 - G1 insomnia

- Best response: SD

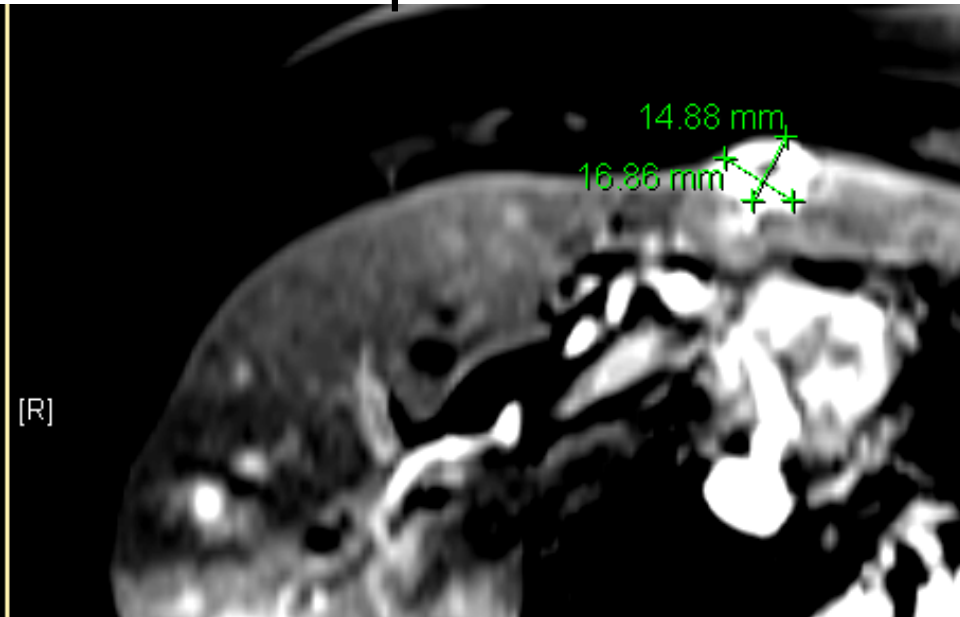
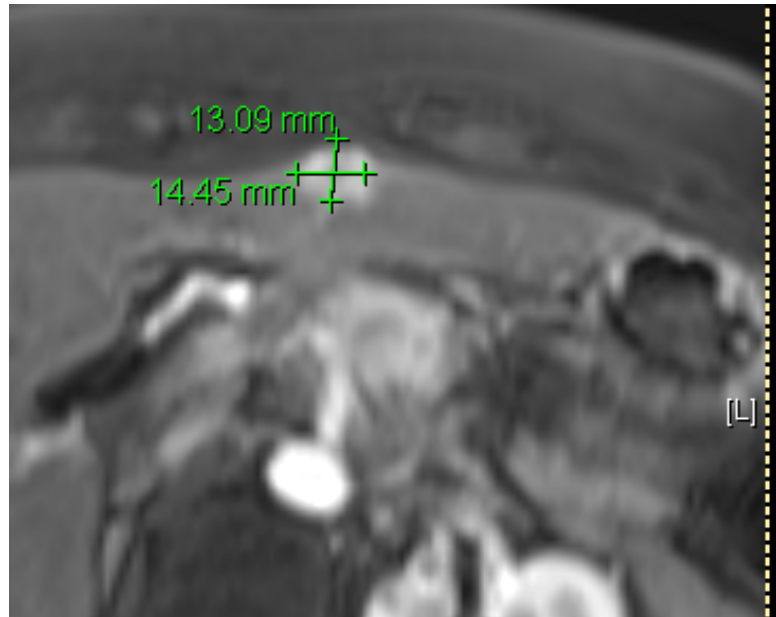
- **PFS: 30 months**

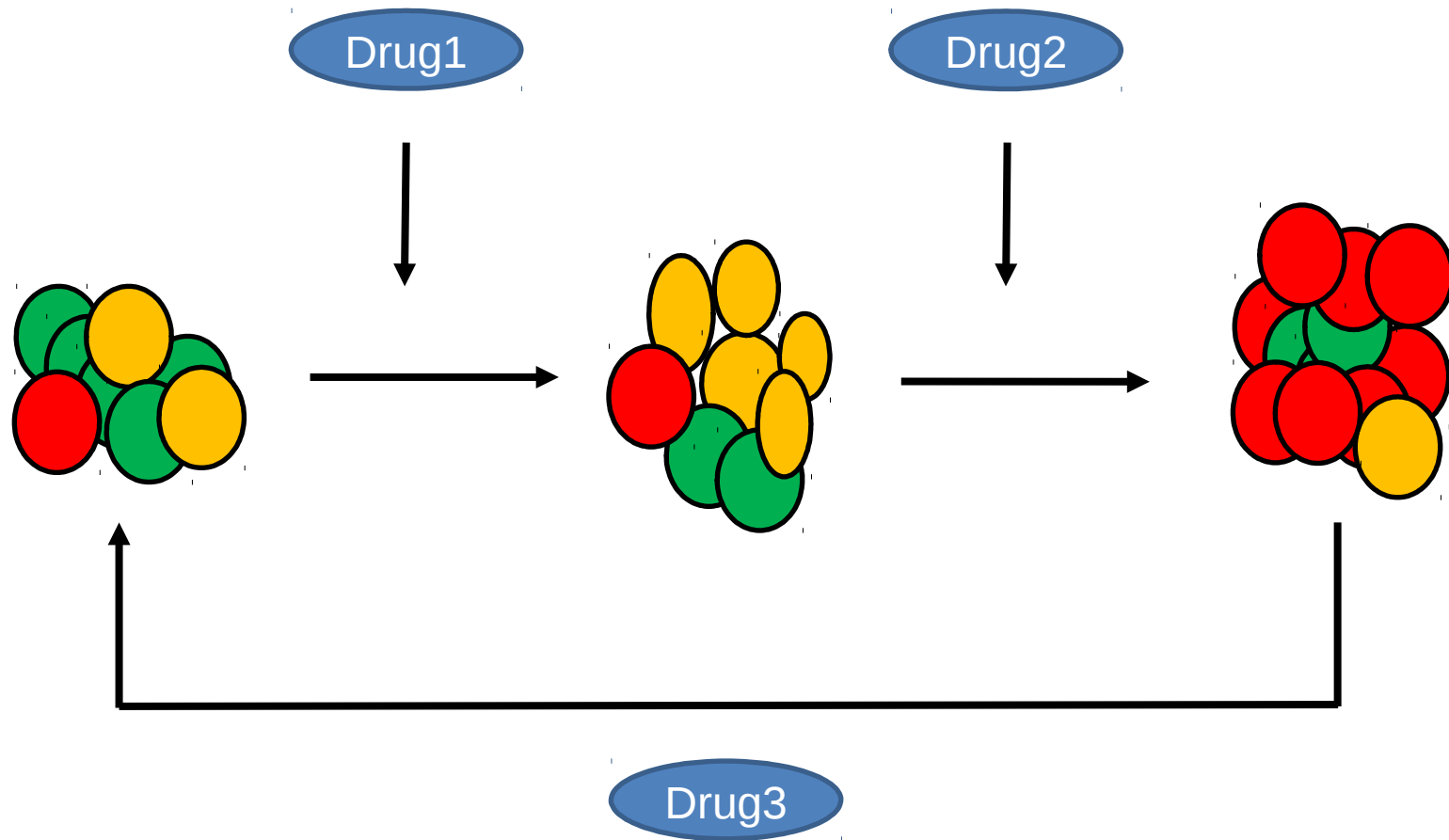


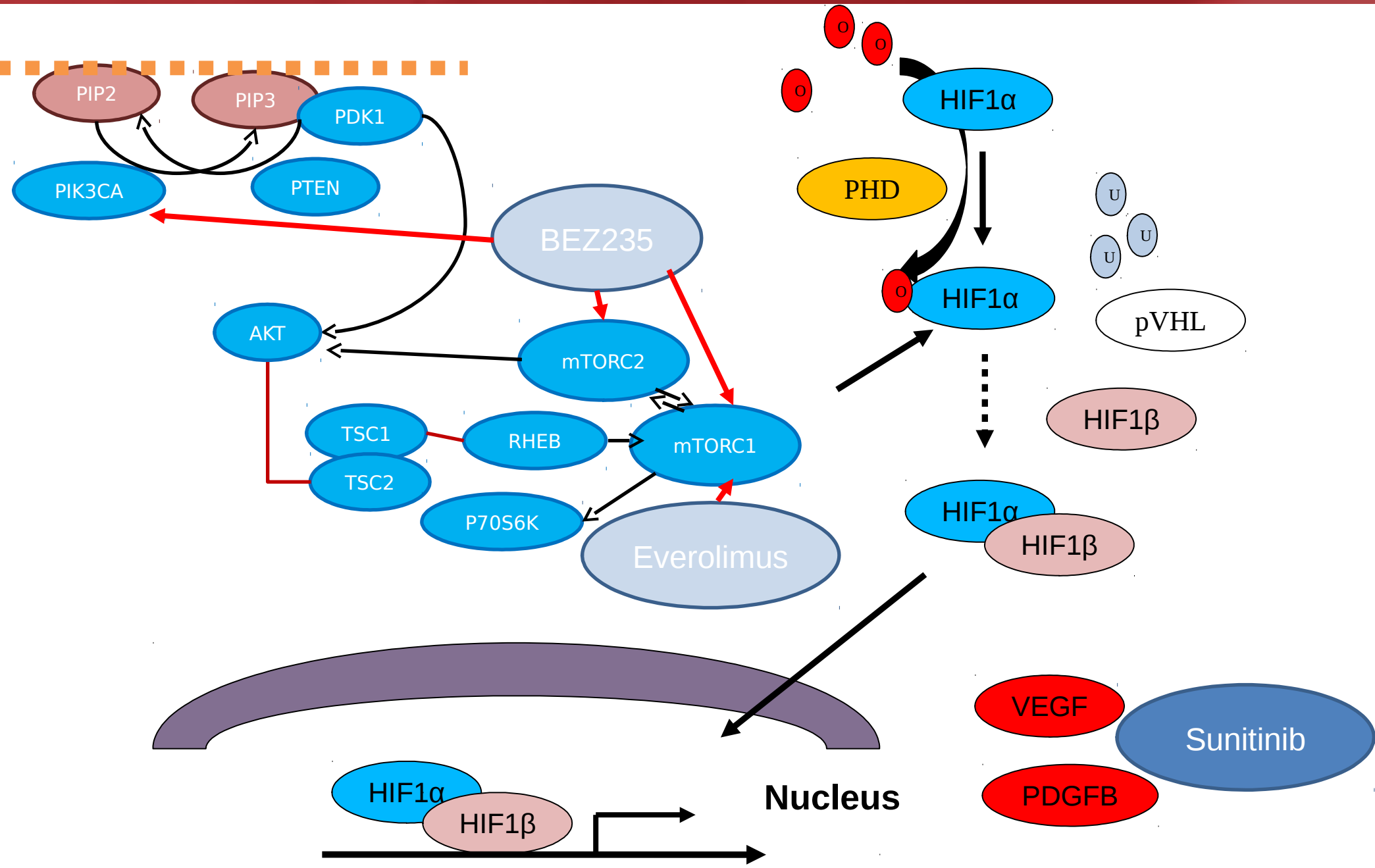
Oct 14



Sept 15







Octobre 2015

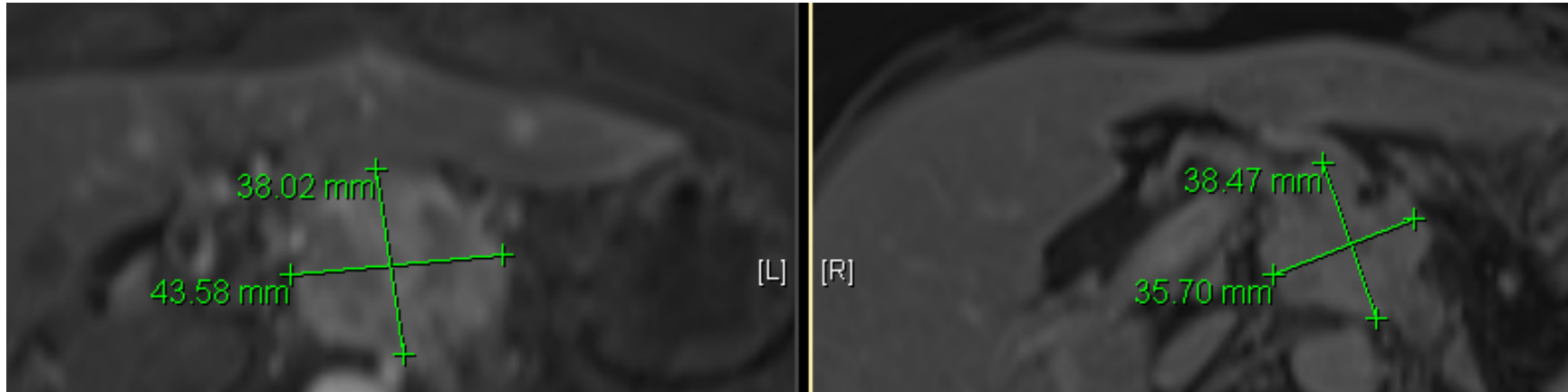
- Considered next line sunitinib 37.5 mg PO OD
- ECOG:1
- Main toxicities:
 - G1 PPE
 - Splinter haemorrhages
- Best response: PR
- **PFS: 11 months**



Table 3. Common Adverse Events in the Safety Population.*

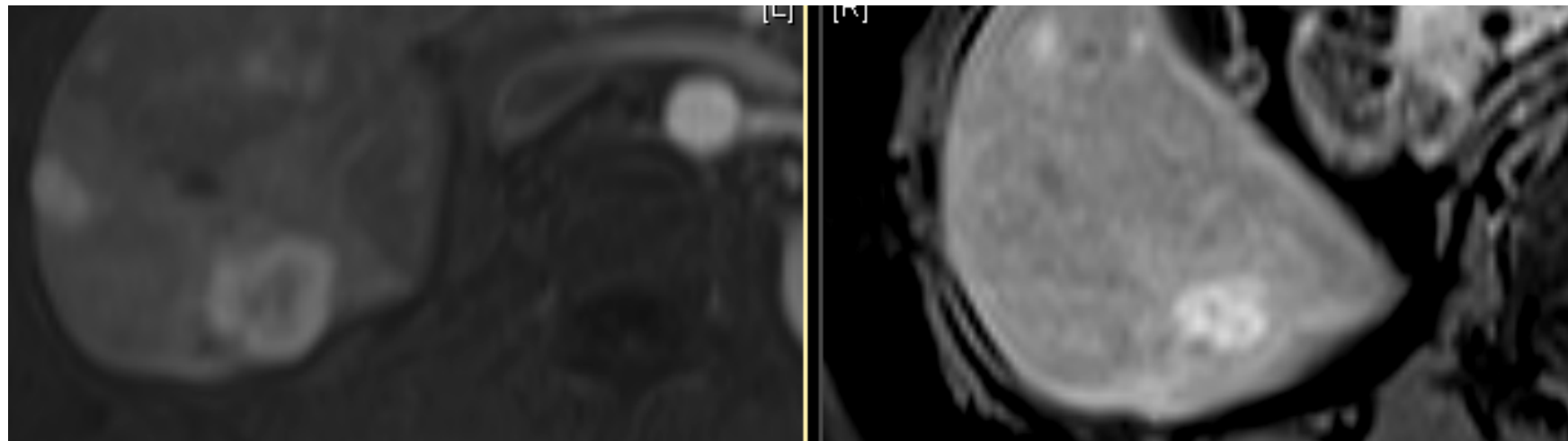
Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	<i>number of patients (percent)</i>					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar-plantar erythro-dysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

* Adverse events were defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Events listed are those of any grade that occurred in more than 15% of patients in either group.



Sept 2015

July 2016



- Patient with pNET in the context of VHL
- Underwent initial management of the residual disease with IFN, then a period of W&W and finally sequential treatment with different drugs.
- The unique features of this disease needed from MDT discussions.
- Several approaches were available at all the key time points.