THERAPY WITH mTOR INHIBITOR IN TWO PATIENTS WITH MALIGNANT PHEOCHROMOCYTOMA

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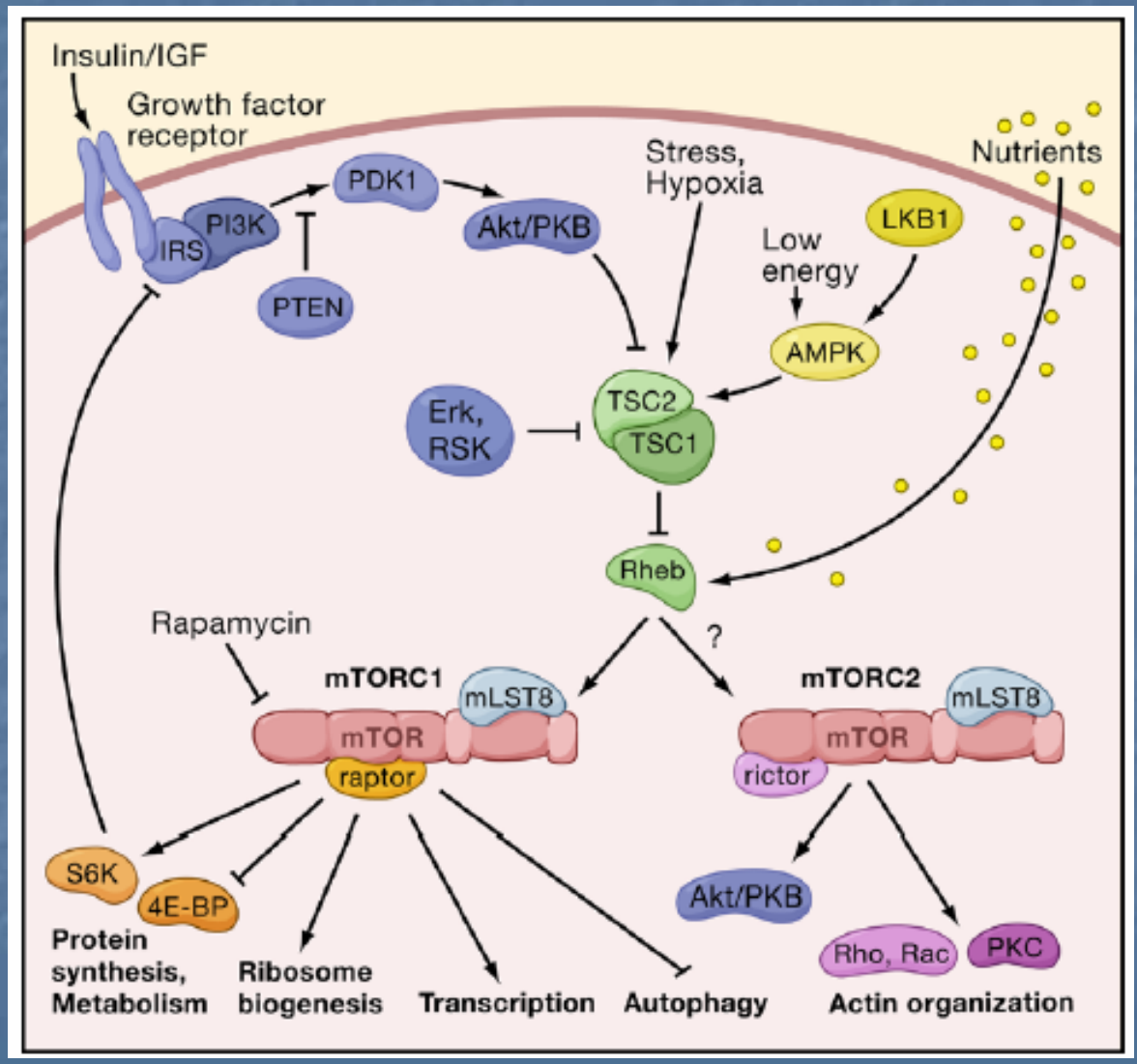
Malignant pheochromocytoma

- An extremely rare neuroendocrine tumor.
- Other than complete surgical resection in selected patients, there is no known effective cure for the disease.

Overview of RAD001

- RAD001 (everolimus) is a novel derivative of rapamycin.
- RAD001 acts as a signal transduction inhibitor by selectively inhibiting mTOR.
- RAD001 has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation.

mTOR signaling in mammalian cell



Stephan Wullschleger,1,3 Robbie Loewith,2,3 and Michael N. Hall1,* Cell 2006

Anti tumor effects of RAD001

- Direct effect: inhibition of tumor cell growth and proliferation (pro-apoptotic).

- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity.

Purpose/Rationale

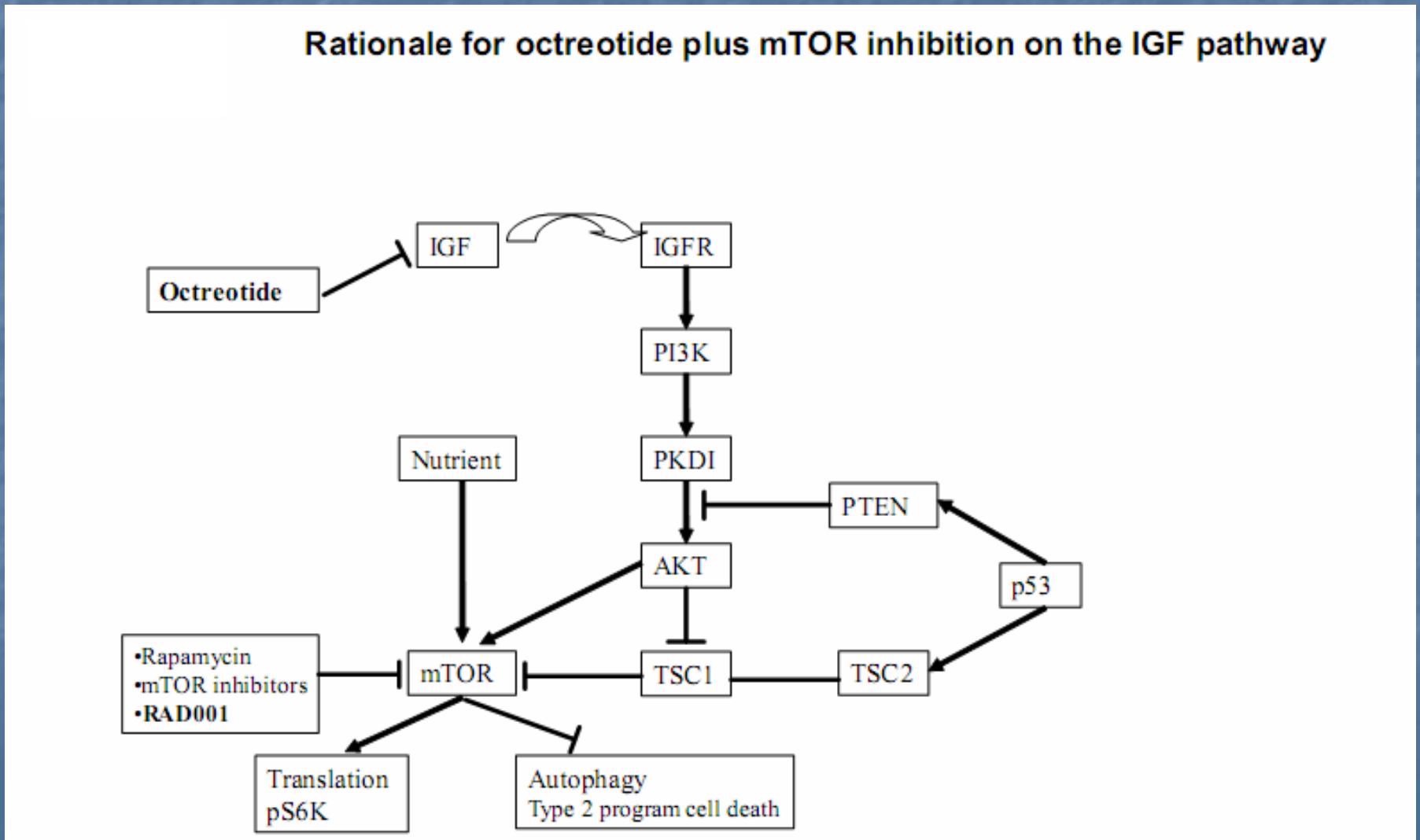
- In-vitro, rapamycin has been shown to inhibit proliferation of human neuroblastoma cells (Misawa, 2003).
- Marked increase in both total and phospho-Akt in pheo's, with no staining in non-malignant adrenal medullae (Fassnacht et al 2005.)

Purpose/Rationale-cont.

- PTEN± transgenic mouse spontaneously develop pheochromocytoma.

- Growth of these tumors was markedly inhibited by treating the animals with mTOR inhibitor (podsypanina, 2001).

Rationale for octreotide and mTOR inhibition on the IGF1 pathway



Preclinical studies with RAD001

- Inhibits proliferation of a range of human tumor cell lines *in-vitro*
- *in vivo* RAD001 selectively inhibits VEGF dependent angiogenic response.
- RAD001 potently inhibits tumor growth, in 11 different mouse xenograft models

RAD001-Adverse Events

	Weekly			Daily		
	5-30 mg n=30	50 mg n=18	70 mg n=38	5mg n=16	10 mg n=45	Total n=147
No. Pts with AEs						
Any event	23 (1)	17 (2)	38 (10)	14 (1)	43 (14)	135 (28)
By event						
Rash	5	8	18	10	27 (1)	68 (1)
Stomatitis/mucositis	6	8 (2)	16 (2)	6 (1)	23 (3)	59 (8)
Fatigue	8	7 (1)	14 (1)	1	17 (1)	47 (3)
Nausea	5	4	8	2	18 (1)	37 (1)
Anorexia	1	6	10	3	15	35
Diarrhea	1	7	7	-	9	24
Vomiting	4	5	5	-	10	24
Headache	7	4	6	6	4	20
Pruritus	2	1	6	3	4	16
Infections[1]	1	3	3 (1)	1	6 (2)	14 (3)
Constipation	-	1	2	2	9	14

RAD001 Laboratory abnormalities

- Myelosupression-
  neutropenia, thrombocytopenia
- Hyperlipidemia–up to 25% (mostly hypercholesterolemia, with rapamycin mainly hyperTG)
- Hyperglycemia-in patients with and w/o DM
- Non infectious pneumonitis-resolves with discontinuation of therapy.

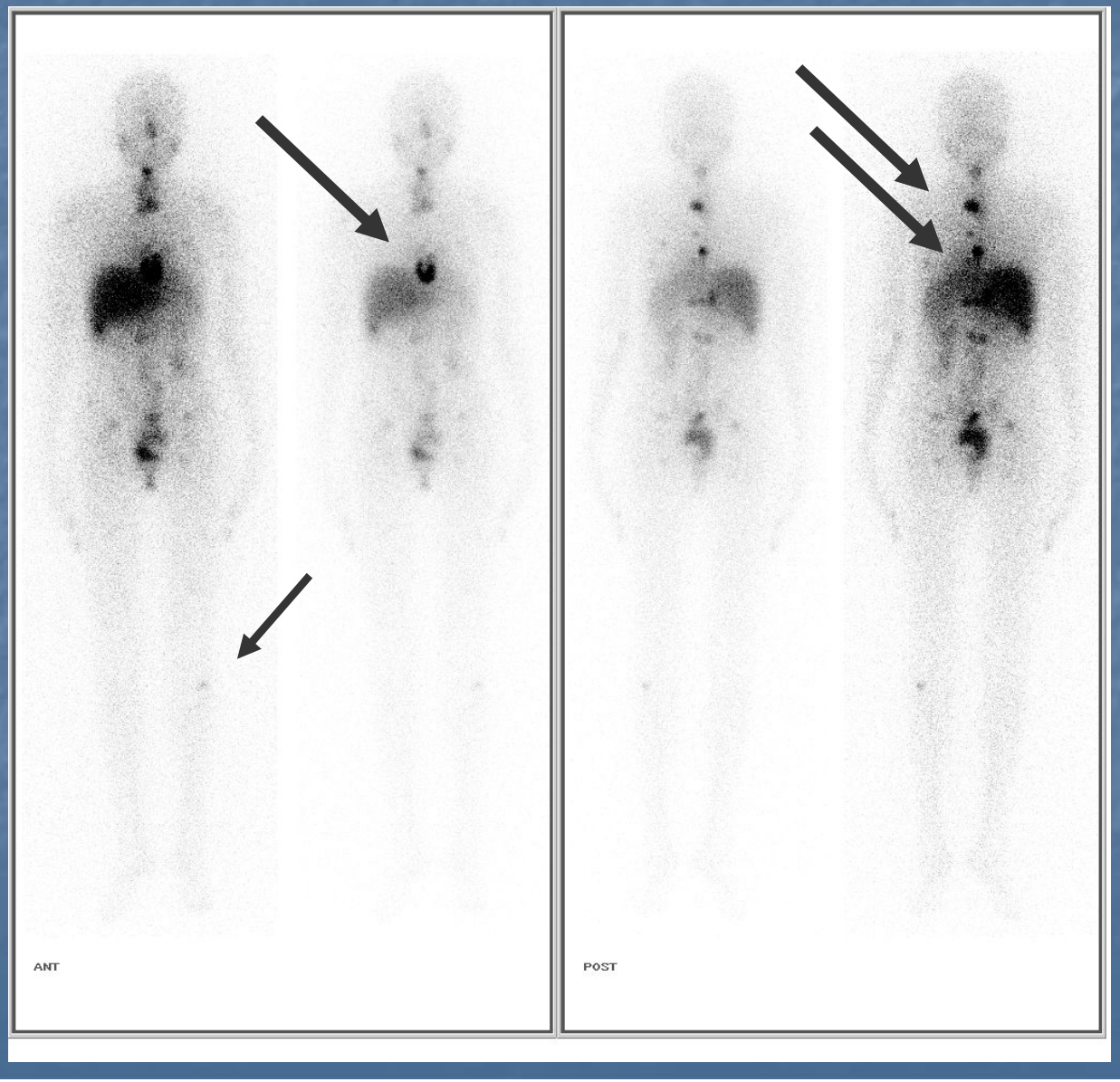
R. D.

- 25 year-old woman, law student
- 14 year history of chest pain, palpitations.
- Age 20- protrusion from sternal area, biopsy- neoplasm (uncharacterized), surgical bx- pheochromocytoma.
- CT- 20 x 15 x 10 cm mass in left adrenal
- Urinary catecholamines- elevated.

R. D.

- Surgery (10/03)- left adrenalectomy & nephrectomy
- Pathology- pheochromocytoma
- MIBG Scan (post-op)-uptake in sternum, lumbar spine, pelvis, rt knee and left lung.

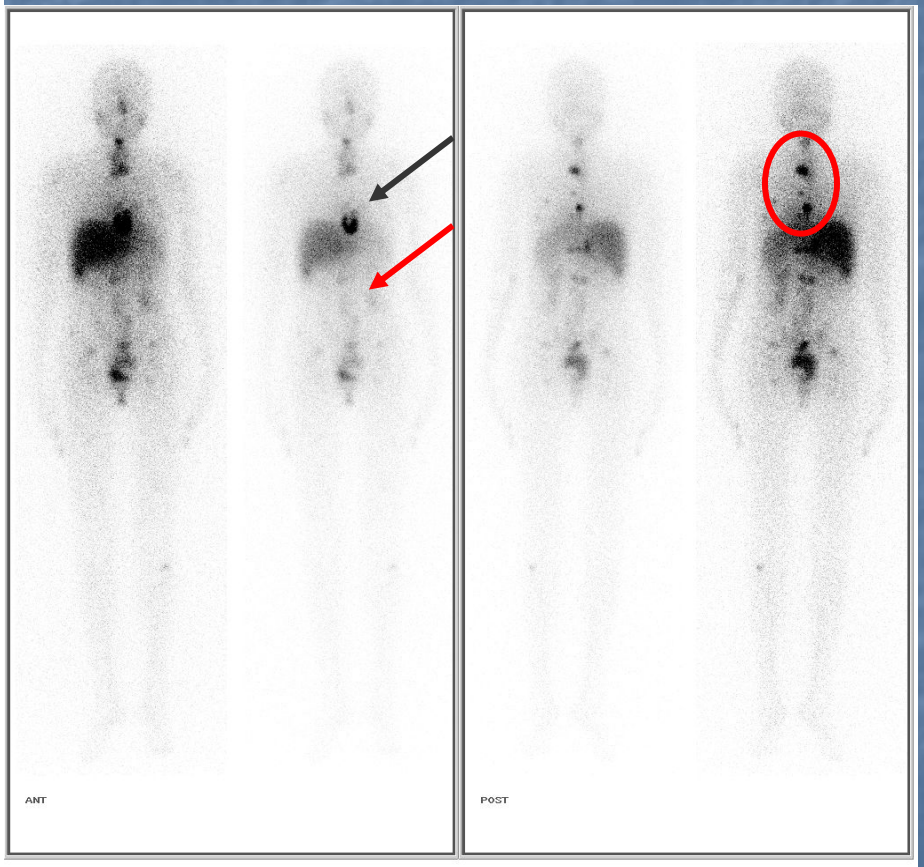
R. D. - MIBG Scan (10/03)

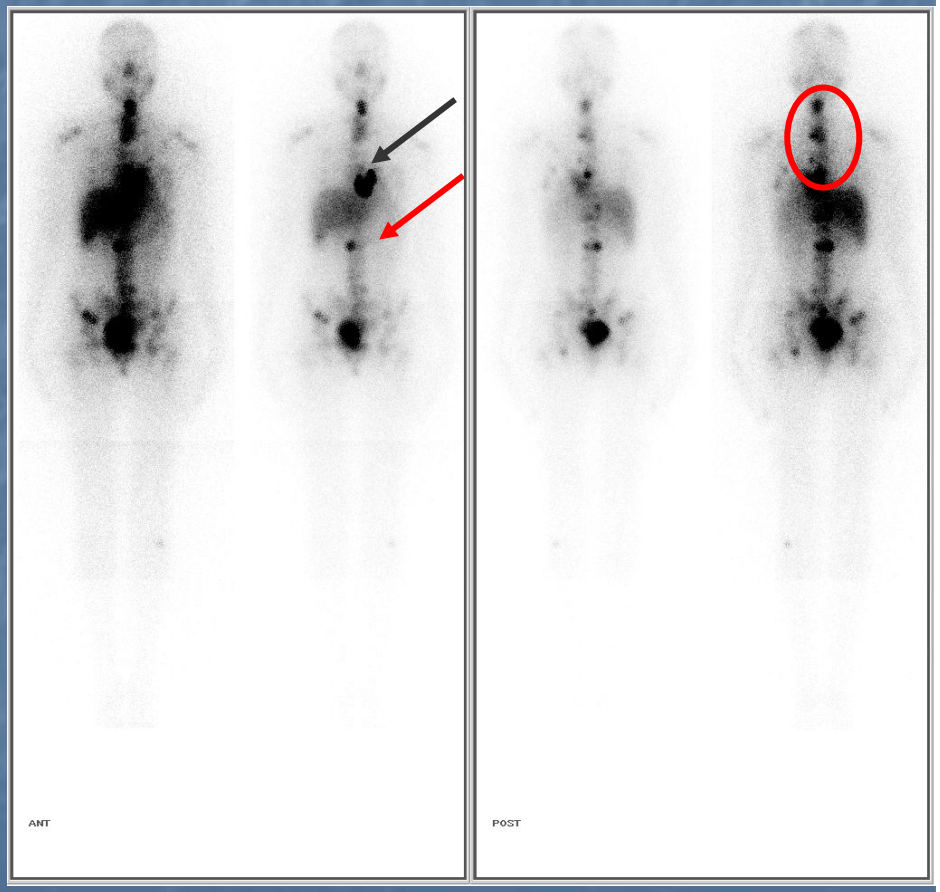


R. D. - MIBG treatments

- Rx:
  - 150 mCi ^{131}I-MIBG x 4 (1/04-10/5)
- Follow up:
  - Urinary catecholamines-normal.
  - MIBG scan- progression
  - Received local radiation to sternum, and rt shoulder.

R. D. - MIBG Scan, post therapy





October 2005

October 2006

Octreoscan-negative (06.2006)

R. D. 2006

- Bone pain→ Irradiation to lumber spine, Zomera.
- Pleural effusion and multiple lung nodules.
- Solid tumor induced hypoglycemia→ glucagon Rx.
- Blood counts suggestive of bone morrow involvement.

R.D: Sep 2006→ March 2007 Chemotherapy

- X7 courses of Chemo (Asaf Harofe):

Cyclophosphamide

Vincristine

Dacarbazine

- Partial response
- Complicated by leukopenia & thrombocytopenia.

R.D.:PET-CT April 2007

- Multiple lesions in lung and pleura.
- Extensive involvement of liver
- Multiple bone lesions: axial and central skeleton.
- LN above and below the diaphragm
- In pelvis-bone, muscle.

R.D-April 2007-RAD001

- 10 mg/day.
- In addition to chemo: vincristine & dacarbazine.
- Sandostatin Lar 30 mg 1/month
- AE's: diarrhea; thromocytopenia, bucal ulcer. Dry cough-pneumonitis?
- Abnormal LFT –transient.

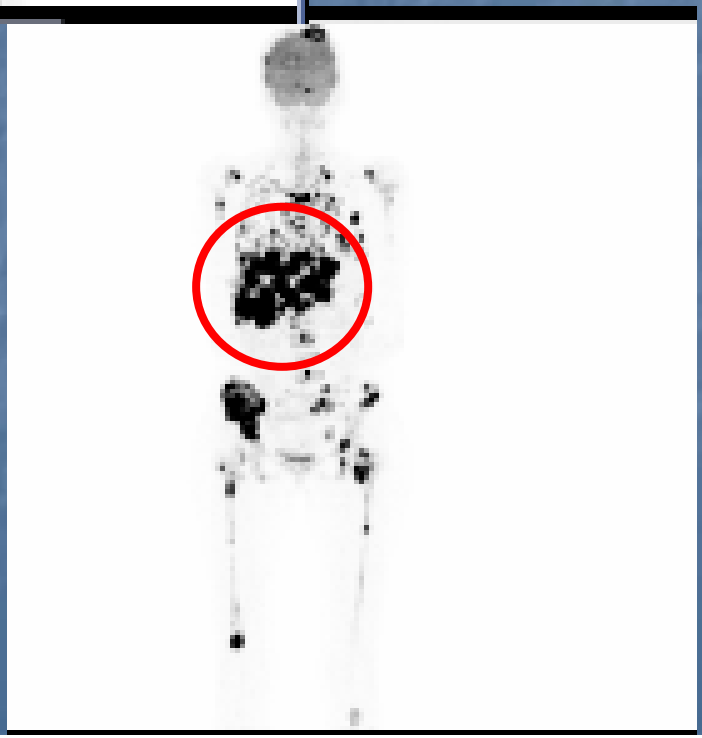
R.D. August 2007

- Progressive disease both by PET and CT
- Progression at all existing sites of disease and new lesions.
- RAD001 was stopped.

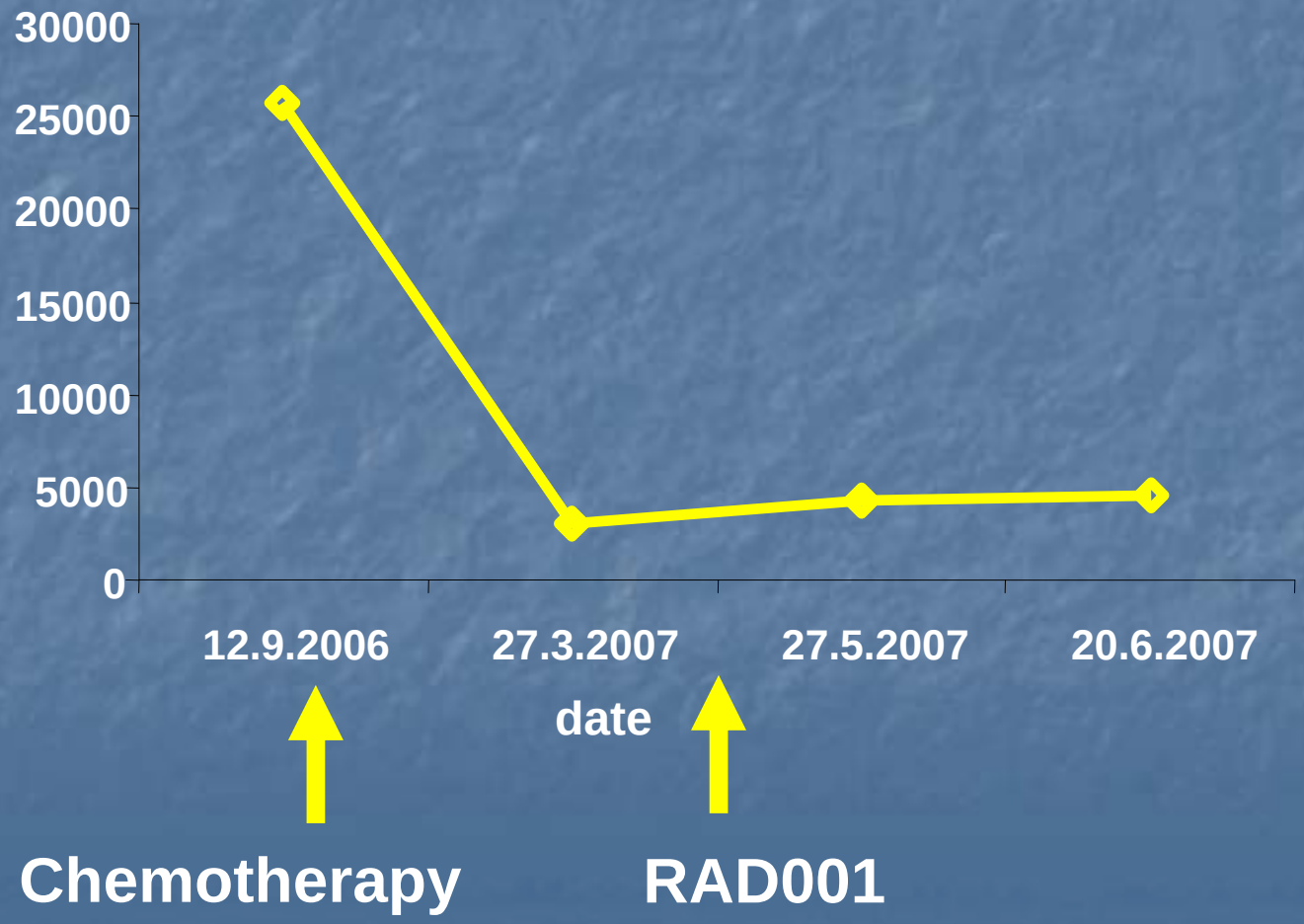
FDG PET

April 2007

July 2007



R.D CgA (N<98 ng/ml)



R.D-Epilog

- Sep 2007-Dec 2007 full dose chemotherapy.
- Patient died.

E.K

- 43 year-old man.
- Past medical history- T2DM (2004) on OHG.
- 2001 - right flank pain.
- CT scan right adrenal mass.
- June 2001 surgery- pheochromocytoma.

E.K- August 2004

- Local recurrence → rt nephrectomy with excision of recurrent tumor.
- Pathology: recurrent multifocal pheochromocytoma with multiple vascular, nephric and peri-nephric invasions.

E.K 2004

- Chemotherpay X6

  Cyclophosphamide

  Vincristine

  Dacarbazine

- No appreciable response.

E.K-2005/6

- Catecholamines in urine X2 normal (2005).
- Pathology-confirmed malignant pheo.
- MIBG- negative
- Octreoscan-negative
- CgA-27.1 ng/ml (normal)

E.K. CT 06/2006, 01/2007

Progressive intra abdominal disease

E. K. March 2007-RAD001

Prior to therapy-

- Microcytic Anemia
- Uncontrolled DM and hyperlipdemia
- Lost 3-4 kg of body weight

RAD001 AE's

- Diarrhea
- Weight loss
- Productive cough
- Worsening of his Anemia (Fe deficiency)
- Abnormal LFT (LDH up to 10000; GTP, ALK phos elevated X5-6 ULN)
- Worsening of DM and hyperlipidemia

RAD001 Rx-follow up

3 months

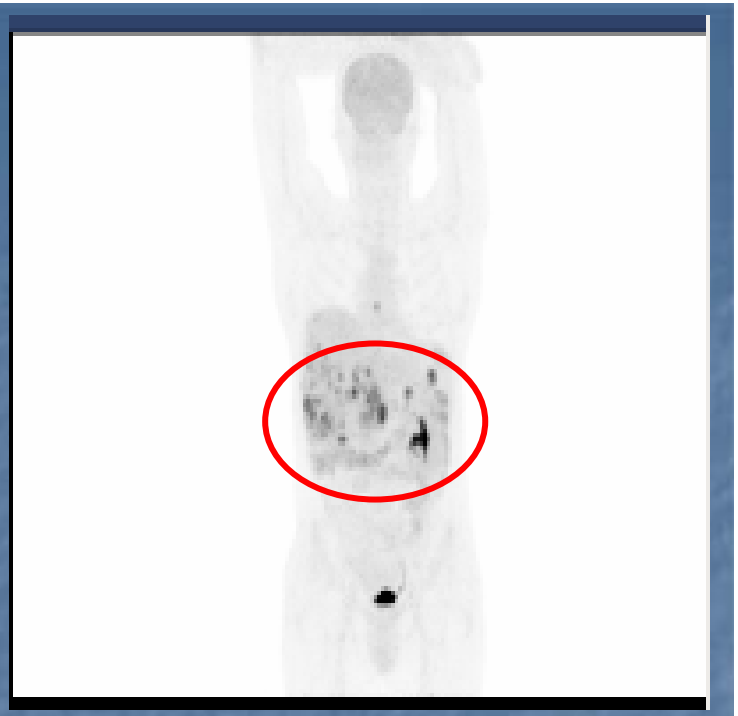
- Stable disease by CT
- Good clinical response

6 months

- Progressive disease by CT and PET
- RAD001 was stopped

FDG PET

July 2007



Dec 2007

E.K. Feb 2008

- Good clinical condition
- Repeat FDG-PET further disease progression
- Negative MIBG

Conclusion

Based on our very limited experience in treating patients with MP with RAD001, one patient experienced initial clinical response and radiological stabilization while the second patient did not show a clear-cut benefit from therapy. Further studies are necessary for assessment of the role of rapamycin derivatives in the treatment of patients with MP.