Advanced Oncology Education Series

Clinical Research Protocols in Oncology: A Systems Approach

Targeted Therapy for Adrenocortical Cancer: From Bench to Bedside

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Targeted Therapy for Adrenocortical Cancer: From Bench to Bedside

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Nothing to Disclose

Topics

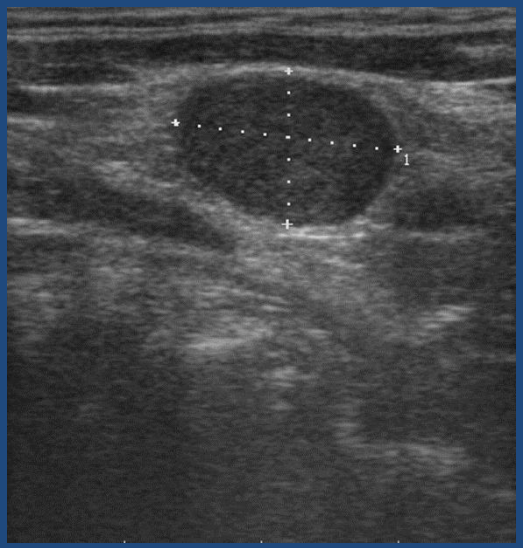
1. Introduction to endocrine neoplasms and Endocrine Oncology Branch (EOB) protocols.
2. Targeted systemic therapy for cancer
3. New protocol for adrenocortical cancer:
   - A Phase I/II Trial of IL-13-Pseudomonas Exotoxin in Patients with Treatment Refractory Malignancies with a Focus on ACC

Introduction to endocrine neoplasms

- Thyroid neoplasms (goiter, nodules, cancer)
- Parathyroid tumors (adenoma, hyperplasia, cancer)
- Adrenal neoplasms
  - Functioning: cortisol, aldosterone, sex hormones, catecholamines
  - Non-functioning
- Pancreatic neuroendocrine tumors
- Paraganglioma

Thyroid Nodules

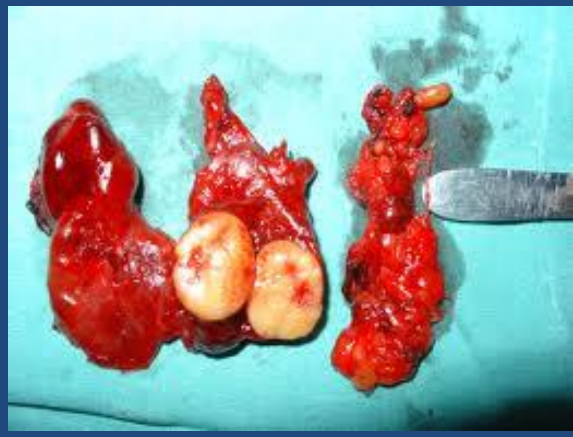
- Palpable thyroid nodules: 4%-7% [1]
- At the age of 55, 45% of women and 32% of men have at least one thyroid nodule.
- Incidentaloma: (<5% are thyroid cancer)
  - 16% of neck CT scan
  - 1.2%-2.3% of FDG-PET scan (30% are thyroid cancer



1. Hedegus. NEJM 2004

Thyroid cancer

- Estimate 60,000+ new cases in 2013: Increased diagnosis of small papillary thyroid cancer.
- ATA guideline: FNA thyroid nodule > 1cm. But small can be mighty.
- Thyroidectomy, lymphadenectomy
- Radioiodine ablation
- 1%-2% mortality: steadily increasing



EOB Protocols for Thyroid Cancer

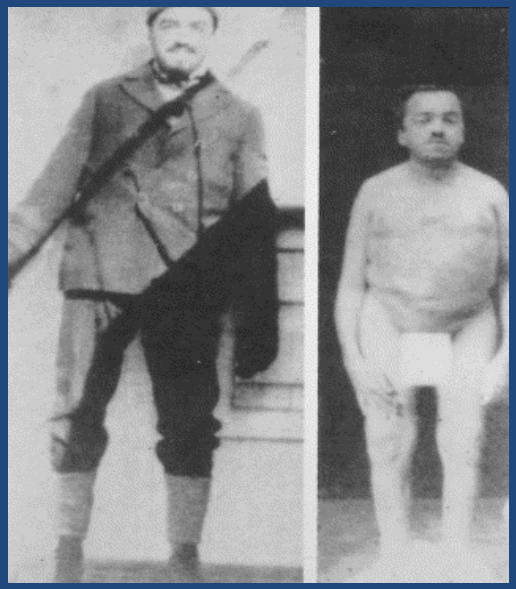
1. Clinical and Genetic Studies in Familial Non-medullary Thyroid Cancer
2. A Phase II Trial of Valproic Acid in Patients With Advanced Thyroid Cancers of Follicular Origin
3. A Phase II Study of Ponatinib in Advanced or Metastatic Medullary Thyroid Cancer

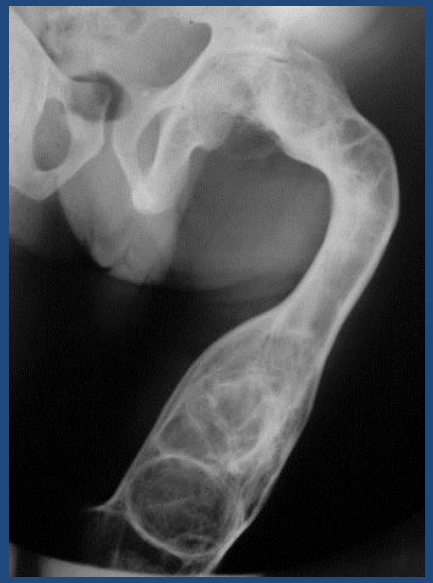
EOB Protocols for Thyroid Cancer

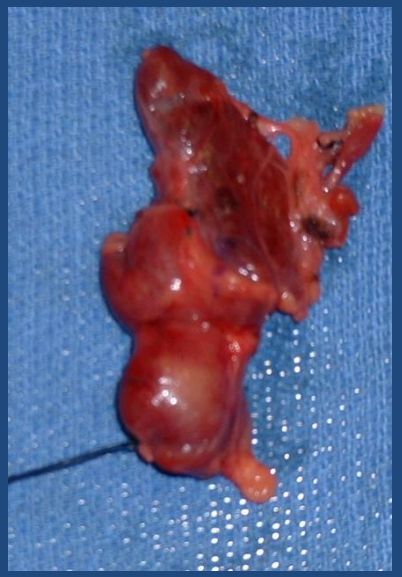
3. A Phase II Study of GI-6207 (CEA Vaccine) in Patients With Recurrent Medullary Thyroid Cancer
4. A Phase I/II Trial of Crolibulin (EPC2407) Plus Cisplatin in Adults With Solid Tumors With a Focus on Anaplastic Thyroid Cancer (ATC)

Primary Hyperparathyroidism

Definition: Inappropriately elevated parathyroid hormone in the presence of hypercalcemia





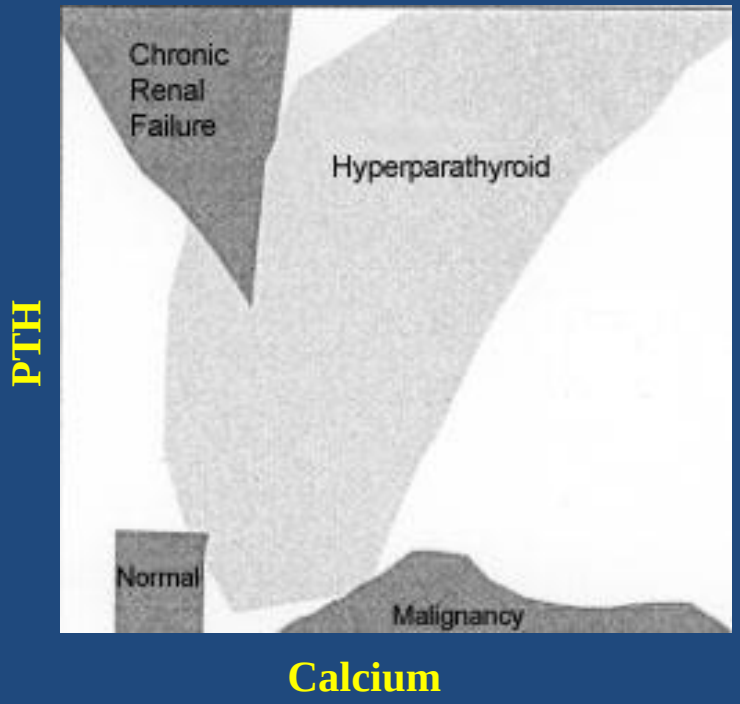


Indications for Parathyroidectomy

- Symptomatic – metabolic complication
- "Asymptomatic"
  - NIH criteria
  - "sub-clinical or non-specific" symptoms
- Parathyroidectomy is the only curative treatment

Asymptomatic Guidelines

Measurement	Guidelines '08
Serum Ca	> 1 mg/dl
24-hr U Ca	Not indicated
Creat clearance	Reduced < 60 ml/min
BMD	*t*-score <-2.5 (any site)
	Previous fracture
Age	< 50



Pancreatic Neuroendocrine Tumors (PNETs)

- Biologically active hormonal production
  - Non-functioning: PP, CGA, NSE, Ghrelin
  - Functioning: gastrin, insulin, glucagon, VIP, CRH
- Inheritance
  - Sporadic:
  - Syndromic: MEN1, VHL, NF-1, TSC

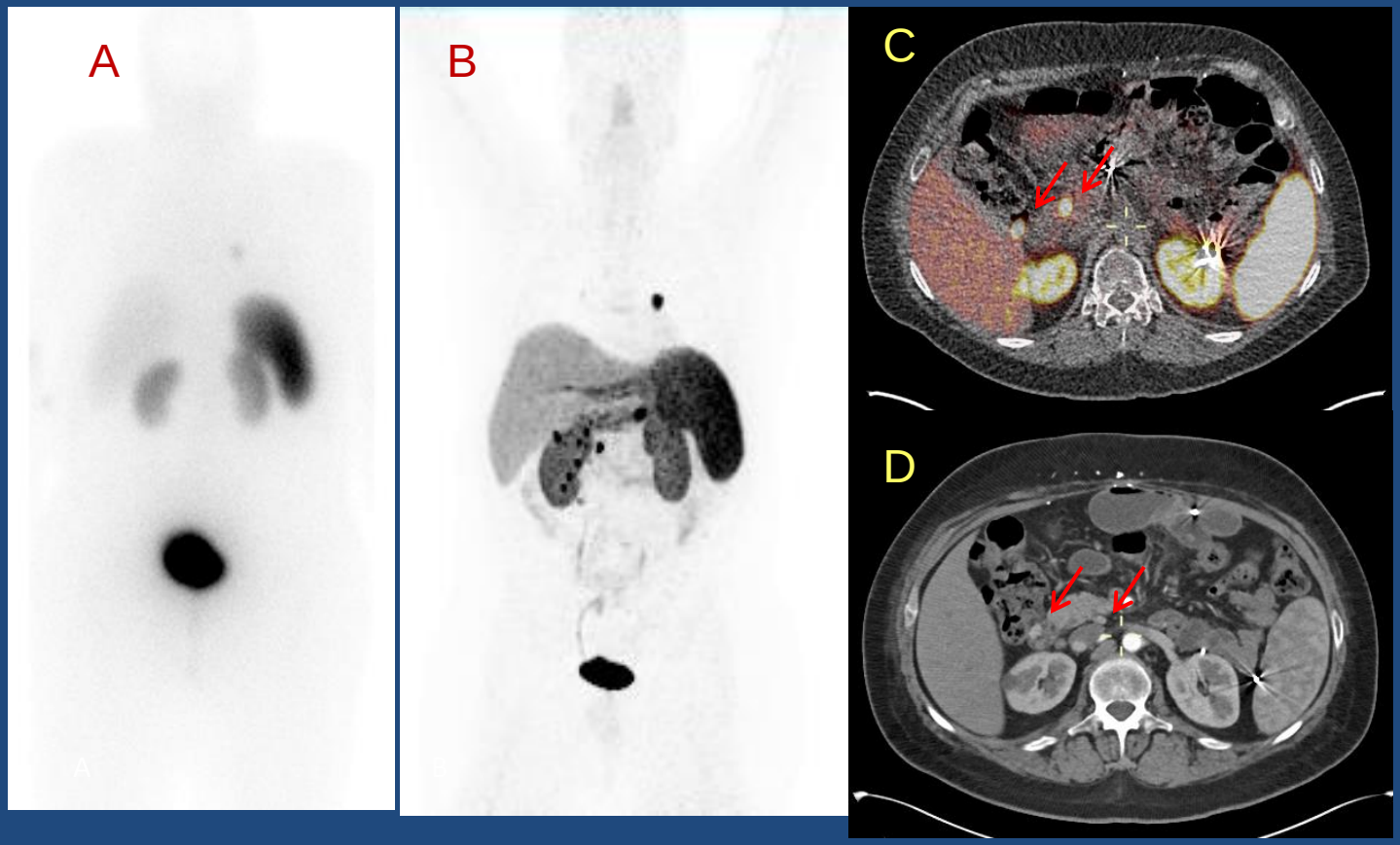
Pancreatic Neuroendocrine Tumors (PNETs)

- Clinical presentation
  - Excessive hormonal secretion
  - Mass effect, invasion, metastasis
  - Incidental finding
- Imaging studies
  - Contrast enhanced CT scan, MRI
  - Functional studies: octreotide scan, FDG-PET
  - Endoscopic ultrasound.

EOB Protocol for PNETs

1. Evaluation of the Natural History and Management of Pancreatic Lesions Associated With Von Hippel-Lindau
2. Evaluation of ^{68}Gallium-DOTATATE PET/CT for Detecting Primary and Metastatic Neuroendocrine Tumors

Octreotide scan vs. 68 Ga-DOTATE

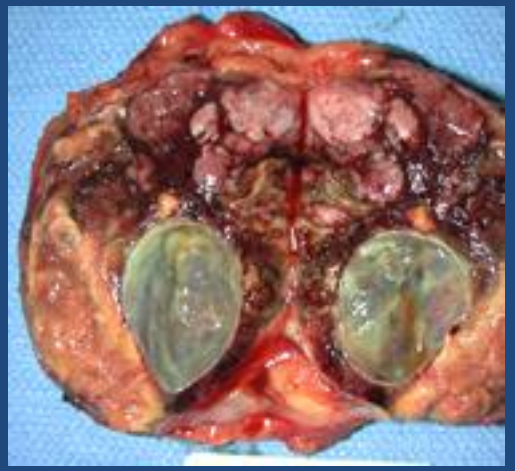


60 yo male with MEN1 and metastatic gastrinoma found on 68 Gallium Dotatate PET/CT

A. Octreoscan with visible lung lesion
B. Dotatate scout with lung lesion and metastatic gastrinoma
C. Dotatate PET/CT with duadenal gastrinoma and a metastatic lymphnode (red arrows)
D. Arterial phase CT with duodenal gastrinoma and metastatic lymphnode (red arrows)

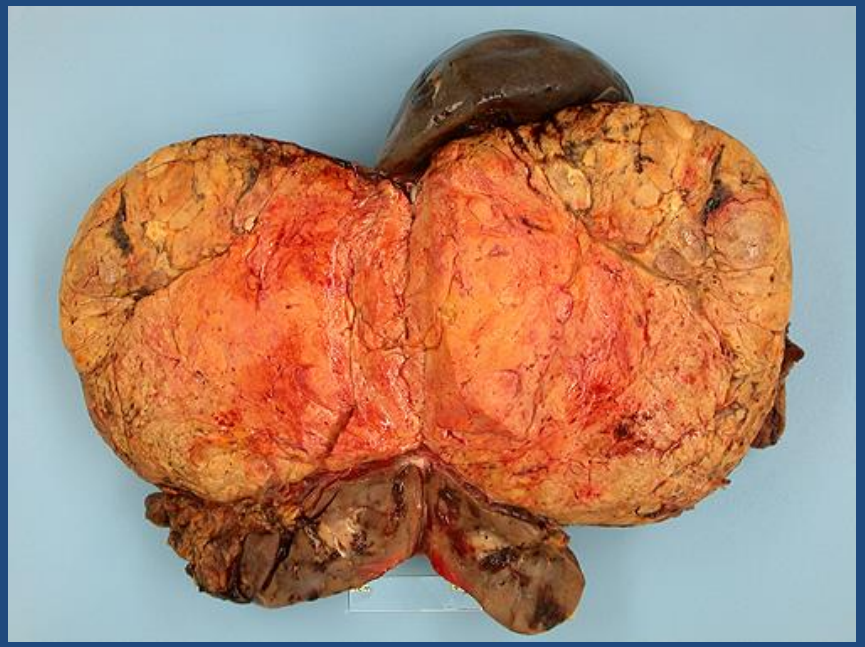
Adrenalectomy

- **Indications**
  - Functioning tumor
    - Pheochromocytoma
    - Cushing's
    - Conn's
  - Nonfunctioning tumor
    - ?risk of primary malignancy
    - ?risk of metastasis



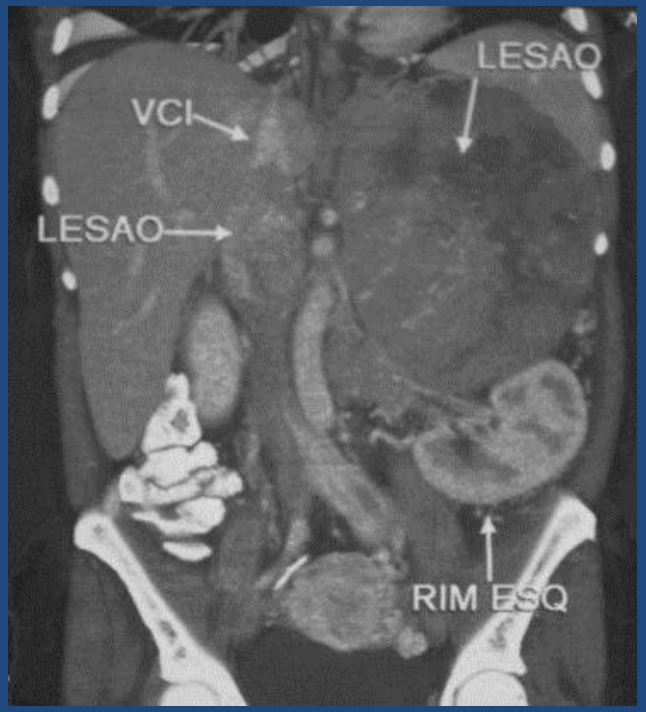
Adrenocortical Cancer

- Rare: 1.5 - 2 per million people per year[1-3].
- Overall 5-year mortality rate of 75 - 90% and an average survival time of 14.5 months[1].
- Presentation: >50% Hypercortisolism is common. Virilizing is rare.



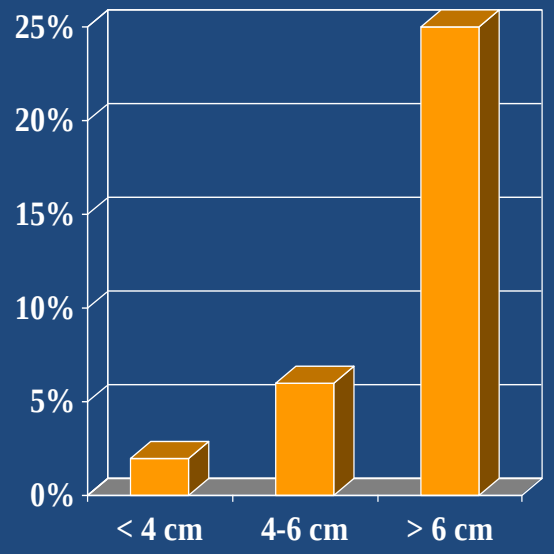
Adrenocortical Cancer

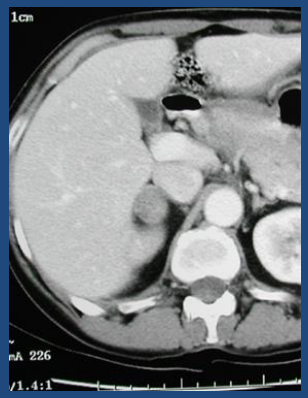
- Mass effects, local invasion
- Incidentally identified.
- Pathological diagnosis (Weiss criteria) can be difficult unless gross invasion or metastasis is present.
- 40% presents with resectable tumor; however, 60% of these die from recurrent disease.

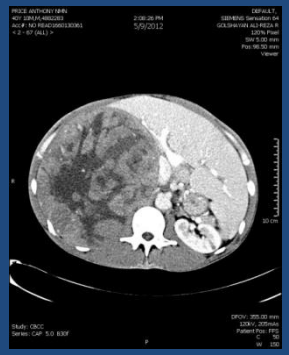


Risk Stratification for ACC by Imaging Studies

- Size is most important
  - >90% of ACC >5cm.
- CT Hounsfield unit >20
- MRI bright on T2 wt
- Heterogeneous (necrosis/calcifications)
- Growing







Adrenocortical Carcinoma

- Poor prognosis
  - Overall 5-year survival of less than 35%
  - 50% 5-year survival for patients with resectable tumors
  - Median survival of <1 year for patients with metastatic disease
  - ***Rare, lethal and neglected!***

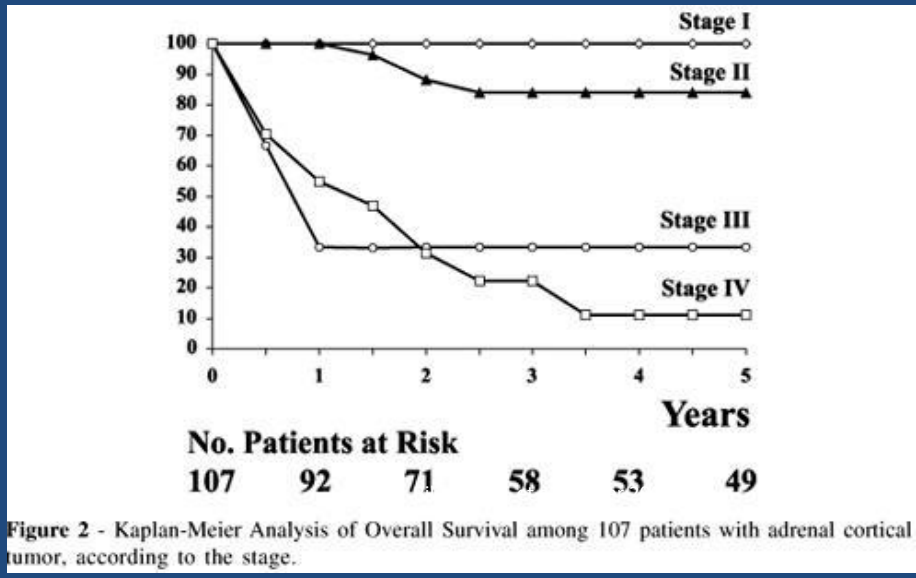


Figure 2 - Kaplan-Meier Analysis of Overall Survival among 107 patients with adrenal cortical tumor, according to the stage.

EOB Protocols for Adrenal Neoplasm

1. Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm.
2. A Phase I/II Trial of IL-13-PE in Patients with Treatment Refractory ACC.

Targeted Systemic Therapy for Cancer

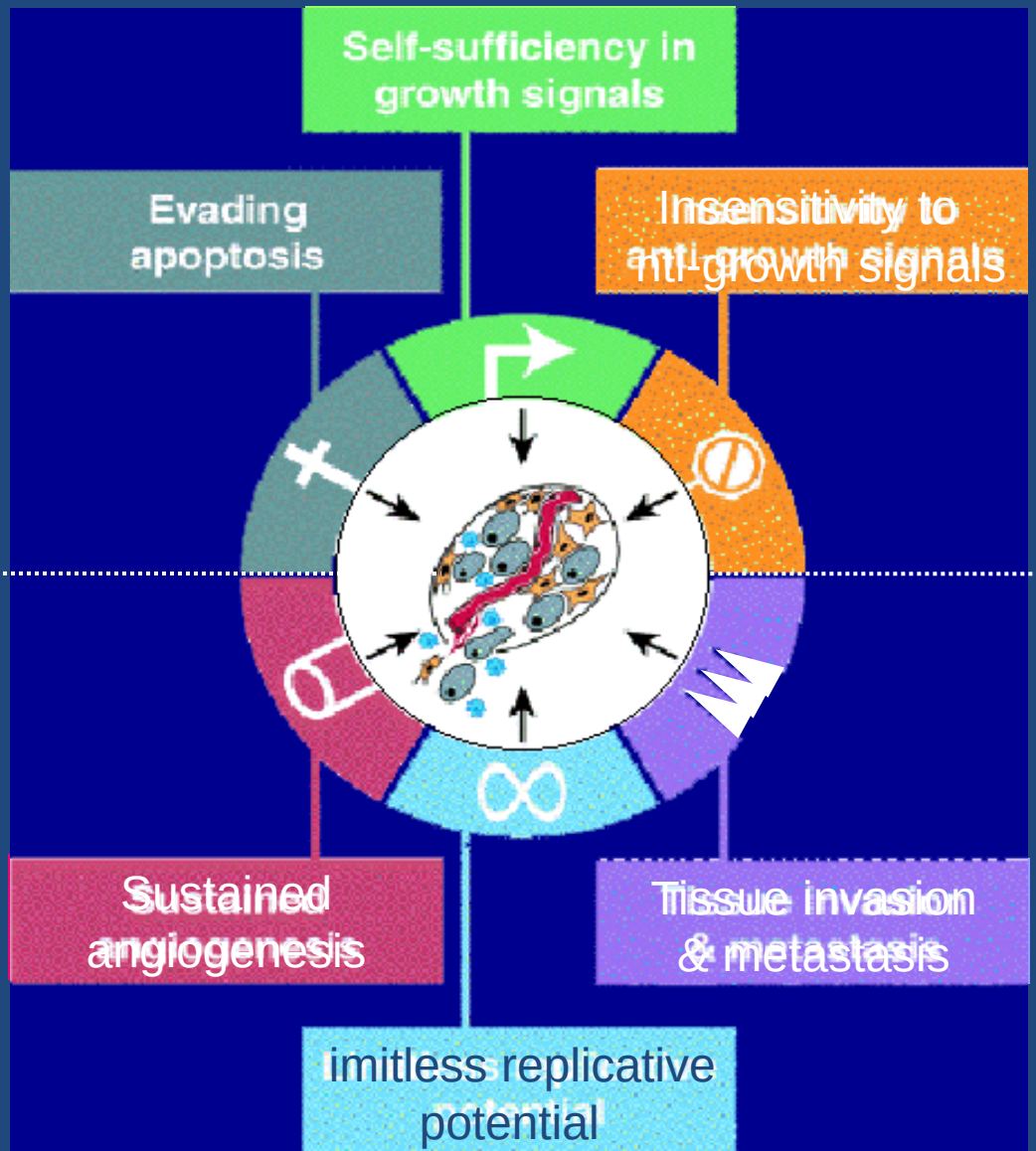
Definition:

- Drugs targeted at pathways, processes and physiology which are uniquely and preferentially expressed in cancer cells:
  - Receptors
  - Genes
  - Angiogenesis
  - Tumor pH

Rationale for Targeted Therapy in Cancer

- Increase therapeutic efficacy:
  - Drug resistance mechanisms in tumor cells.
  - Utilize unique characteristics of tumor cells to enhance drug delivery→ maximize effects.
- Reduce systemic toxicity:
  - Effective drug delivering system
  - Tumor specific targeting system→ enhancing tumor tissue level, reducing toxicity.

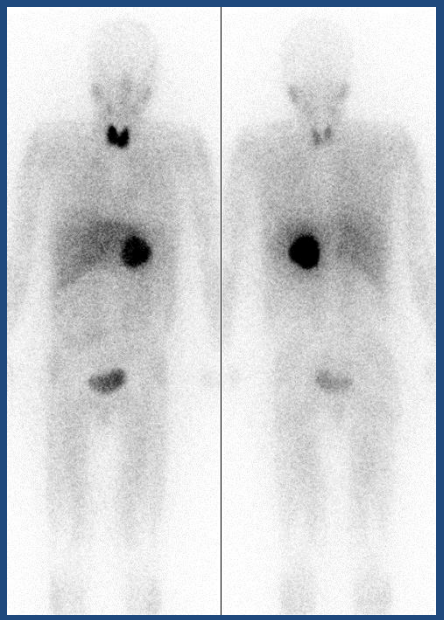
Six Essential Alterations in Cell Physiology in Malignancy: Targets for Novel Drugs

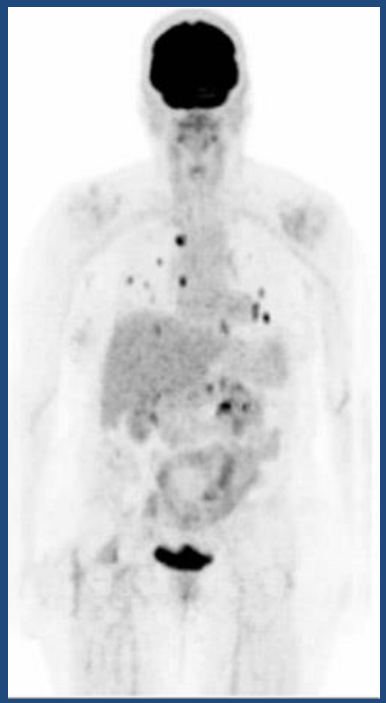


Hanahan & Weinberg, *Cell* 100:57 (2000)

Radioiodine Ablation in Thyroid Cancer

- *Is* a targeted therapy for differentiated thyroid cancer
- Utilize unique ability to concentrate iodine of thyroid cancer cells.





The Ideal Targets

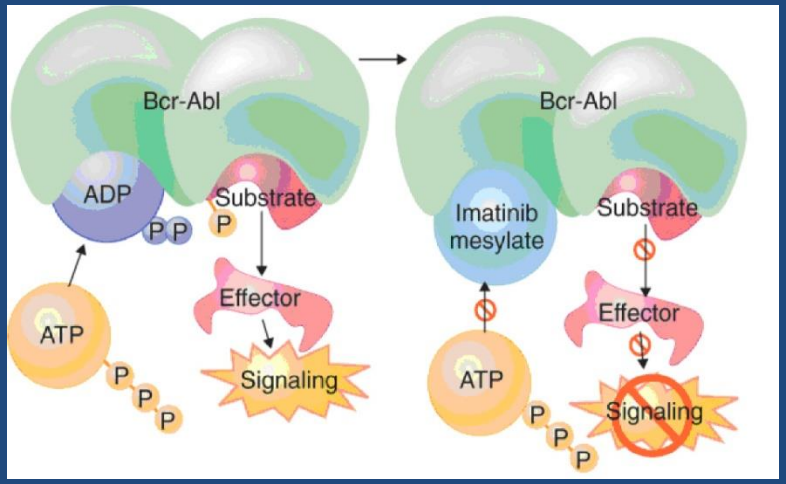
- Highly expressed and prevalent in cancer, low in other tissues.
- Critical for desire phenotypic effects (cell proliferation, apoptosis, metastasis).

Existing Targets used Clinically.

- RET-tyrosine kinase: medullary thyroid cancer, PNETs
- c-Kit: for GIST
- bcr/Abl: for CML
- Steroid receptors: for ER+ breast cancer, prostate cancer, and lymphoma
- HER2: for breast and gastric ca
- CD20: for B-cell lymphoma
- B-RAF: for melanoma

Imatinib Mesylate in CML

- Bcr-abl is the root cause of CML which is considered a “monogenetic disease”
- Imatinib Mesylate specifically targets the bcr-abl tyrosine kinase.



Imatinib Mesylate in CML: Response

- 55% of patients with CML-blast crisis and 70% of ALL-blast crisis patientresponded
- 10.5% of CML and 20% of ALL patients had complete remission

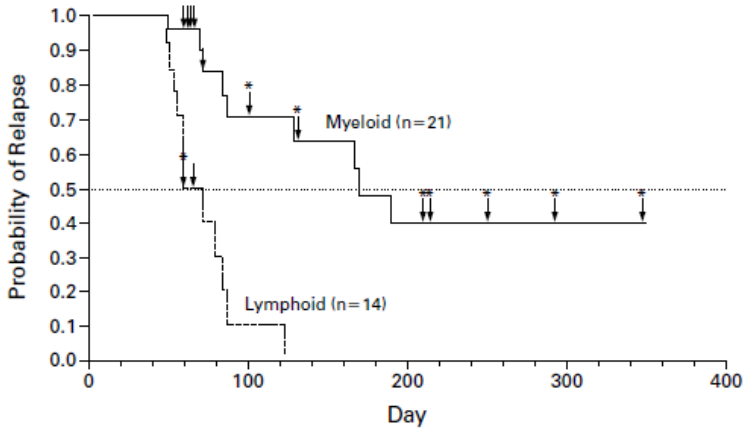


Figure 2. Time to Relapse in Patients with Myeloid or Lymphoid Blast Crisis Who Had a Response to STI571.

Arrows with asterisks indicate patients still enrolled in the study and in remission at the time of the last follow-up; arrows without asterisks indicate the day on which patients were removed from the study.

B. Druker et al, N Engl J Med *2001*

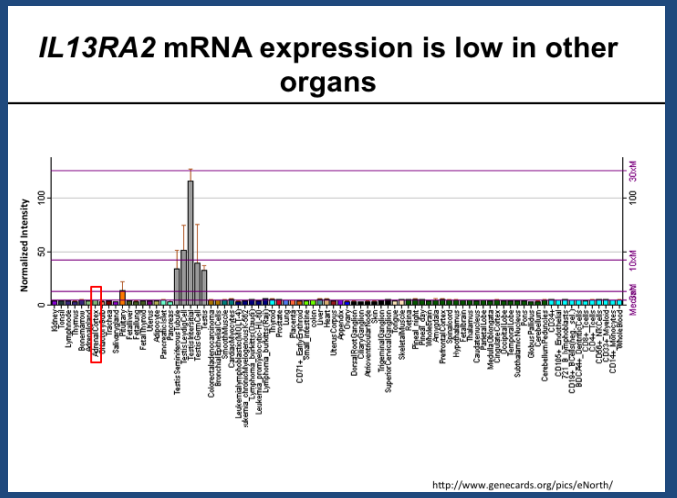
Targeted Therapy in Solid Tumors: Limitations

- Most solid tumors have complex genetic abnormalities→ genetic heterogeneity.
- Molecular and pathway heterogeneity.
- Hitting one narrow target is not likely to be that beneficial.

A Phase I/II Trial of IL-13-Pseudomonas Exotoxin in Patients with Treatment Refractory Malignancies with a Focus on ACC

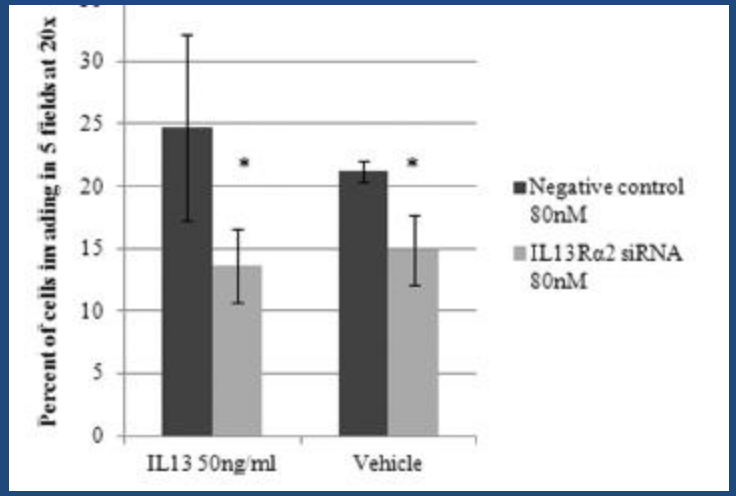
IL13Rα2 as a Candidate Target

- Genome-wide expression analysis of adrenocortical tumors demonstrated overexpression of Interleukin-13 receptor subunit alpha-2 (IL13Rα2) in ACC.
- Low or absent expression of IL13Rα2 in normal cells and tissues
- IL13Rα2 is a high-affinity receptor of Th2-derived cytokine interleukin -13 (IL-13).

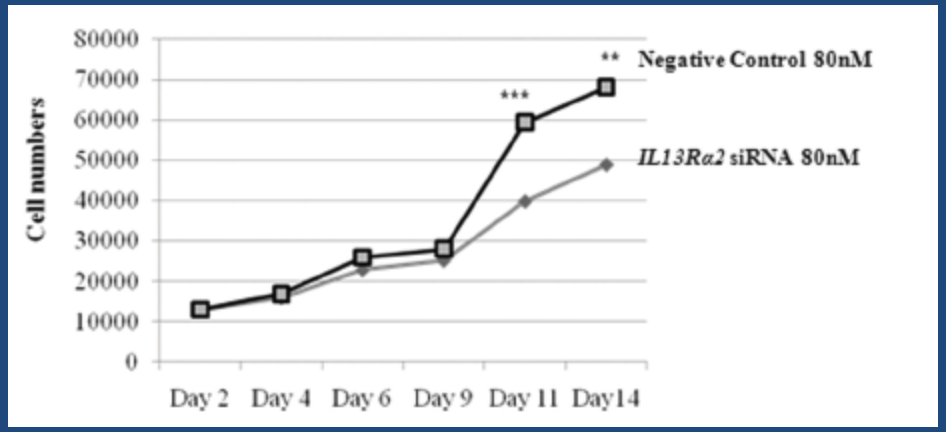


Functions of IL13Rα2 in ACC

- IL-13 signals through IL13Rα2 and influences ACC cell invasion

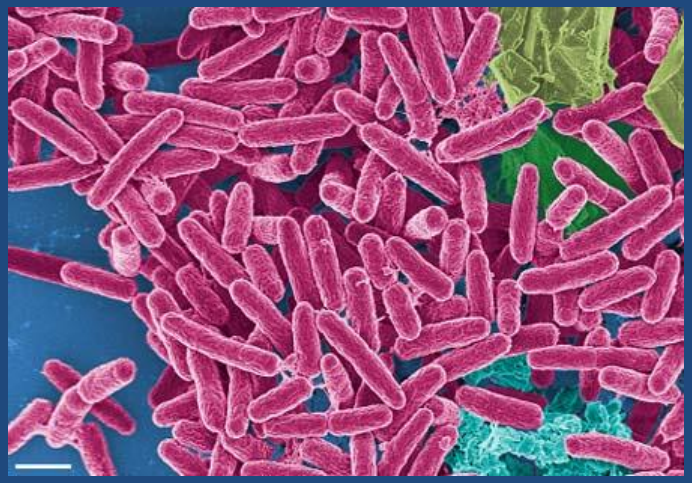


- IL-13 signals through IL13Rα2 and influences ACC cell proliferation



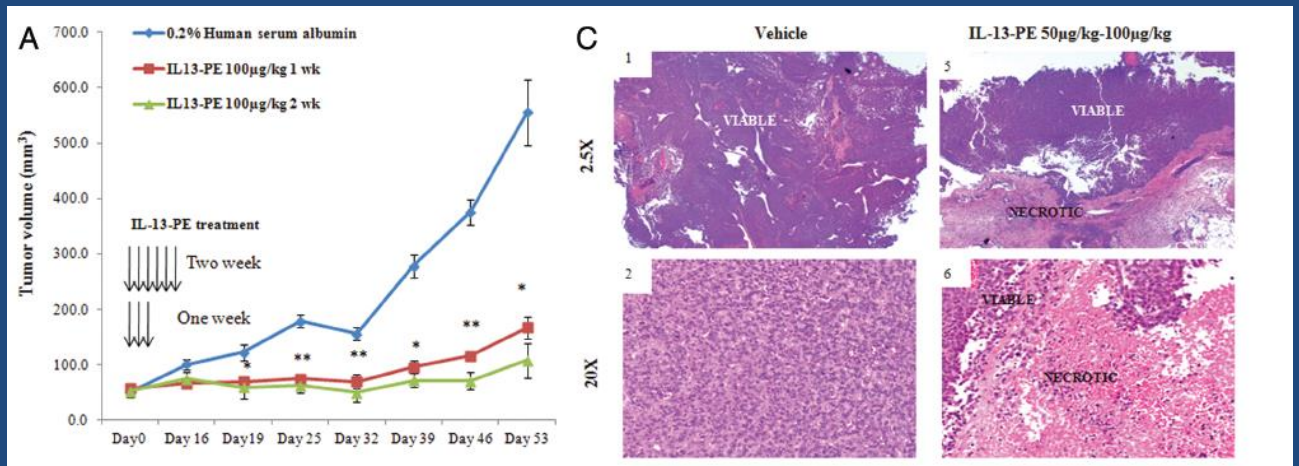
IL-13 Pseudomonas Exotoxin

- A chimeric fusion of recombinant ligand-targeted cytotoxins, *Pseudomonas exotoxin A,* and IL-13
- In phase I trial of IL-13 PE in 12 patients with metastatic renal cell carcinoma, 3 developed acute renal failure at 4 ug/kg.



Pre-clinical Studies in ACC

- IL13-PE is effective in ACC cells (NCI-H295R) and a renal cell carcinoma cells(PM-RCC) and specific to cells that express IL13Rα2, siRNA knockdown of IL13Rα2 in NCI-H295R cells resulted in a loss of sensitivity.
- *In vivo* study of IL13-PE in ACC xenografts: 50%-70% reduction in tumor sizes and increased survival with no observed toxicity.



Study Objectives and Eligibility

- Objectives
- Safety and maximal tolerated dose of IL-13-PE
- Response rate, and progression-free survival
- Tumor response
- Association with IL13RA2 expression

- Eligibility
- > 18 years of age
- Pathology confirmed tumors with IL13RA2.
- Measurable disease
- Last treatment > 4 weeks
- Mitotane is allowed.

Study implementation

- Pre-treatment evaluation
  - Tumor (+) for IL13RA2 by IHC
  - Axial imaging studies and FDG-PET scan
  - Check human PE antibody
  - Acceptable lab values
  - Baseline EKG.
- Drug administration
  - Starting 1 ug/kg IV, will be escalated up to 3 ug/kg.
  - Day 1,3,5 of a 4 week cycle, up to 4 courses
  - IV hydration before and after infusion.

Monitoring

- Allergic reaction:
  - Q2H vital signs during infusion then Q4h for 24h
- Kidney function:
  - **24-hr urine for creatinine clearance and UA**
  - **Serum creatinine**
- Evidence of thrombotic microangiopathy
  - Low plts, anemia, kidney injury
- Heart: EKG baseline and 2h post infusion
- Systemic toxicity:
  - CBC, BMP, LFTs
- Human PE antibody:
- Pharmacokinetics:
  - Blood: Days 1 and 3 of course #1 and on Day 1 of course #2.

Thank You.

- “To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.”
  Albert Einstein