Recent Advances in Treatment of Multiple Endocrine Neoplasia Type 1 (MEN1) Tumours

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AMEND

(Association for Multiple Endocrine Neoplasia Disorders)
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Draycote Hotel, Rugby

Multiple Endocrine Neoplasia Type 1 (MEN1) Tumours

Parathyroid adenomas

Pancreatic (islet) neuroendocrine tumours (PNETS)

Pituitary (anterior) prolactinomas, somatotrophinomas

Thymic, bronchopulmonary and gastric NETs (carcinoids)

Adrenal adenomas (secreting cortisol or aldosterone or non-secreting)

Lipomas

Collagenomas

Fibromas

Treatment of MEN1 Parathyroid Tumours

- Surgery, performed by an experienced endocrine surgeon is treatment of choice
- Conventional open bilateral exploration with subtotal parathyroidectomy (at least 3.5 glands) or total parathyroidectomy is recommended
- Concurrent transcervical thymectomy is also suggested
- Minimal invasive parathyroidectomy is not recommended because multiple glands are affected
- Optimum timing has not been defined
- Drugs, e.g. calcimimetics which act via calcium-sensing receptor may be used if surgery has failed or is contraindicated

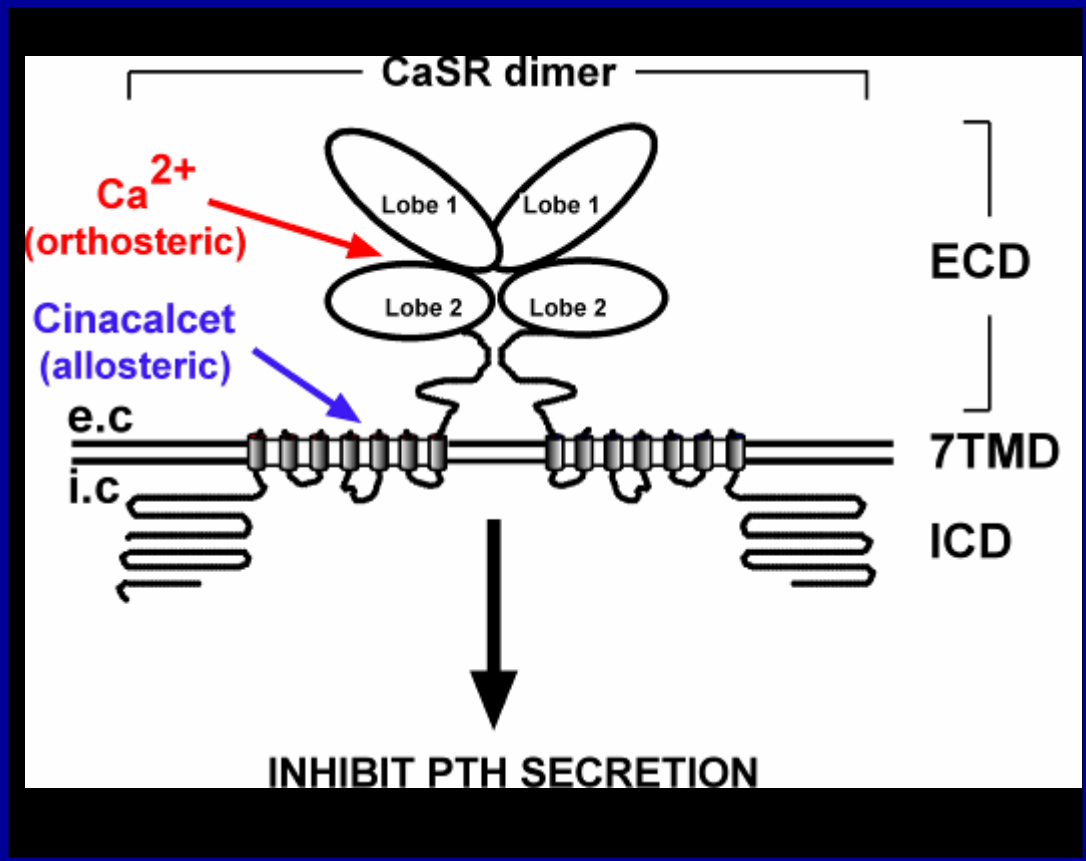
Cinacalcet is a positive allosteric CaSR modulator

- Cinacalcet binds to CaSR transmembrane domain and stabilizes the receptor in an active conformation

- Decrease serum calcium and PTH concentrations

- Licensed for treatment of
1)Secondary hyperpara-thyroidism in end-stage renal failure
2) Metastastic parathyroid carcinoma
3) Inoperable primary hyperparathyroidism

Binding of orthosteric and allosteric CaSR agonists



Pancreatic Neuroendocrine Tumours (NETS)

AIMS

- **Maintain disease and symptom-free for a good quality of life, as long as possible**

- **Achieve cure by surgery, if possible for functioning pancreatic NETS e.g. insulinomas**

Role of surgery for treatment of gastrinomas and non-functioning NETS is controversial

Evaluate extent of disease fully prior to planning any specific therapy

Treatment of Pancreatic NETS - Gastrinomas

- Surgery for non-metastasising gastrinoma arising in pancreas may be curative, as long as it is performed by an experienced endocrine surgeon

- Optimal treatment – controversial, as there are open multiple small duodenal gastrinomas

DRUGS: Proton-pump inhibitors (± somatostatin analogues)

SURGERY: Experienced centres report good results with local excision of tumours and lymph node dissection, duodenectomy, or duodenopancreatectomy

Treatment of Pancreatic Non-Functioning NETS

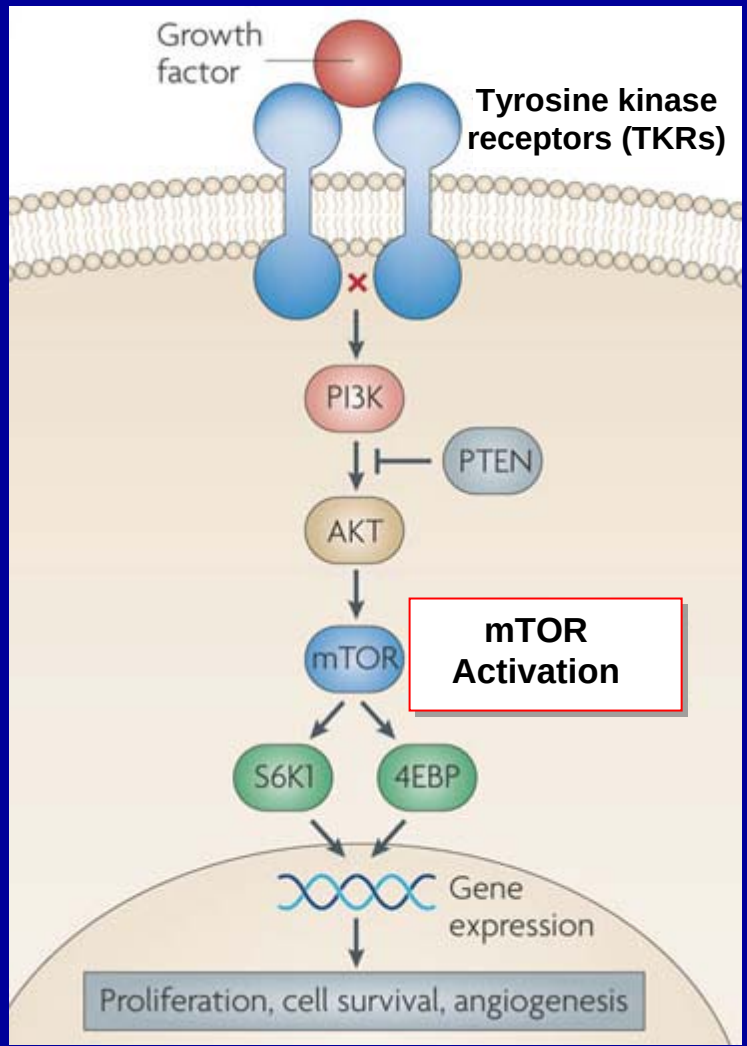
- Controversial
- Surgery for tumours >1cm in size and/or demonstrate significant growth over 6-12 months

Treatment of non-resectable tumours:

- Somatostatin analogues
- Biotherapy
- Targetted radionucleotide therapy
- Chemotherapy
- Emerging treatments

Emerging Treatments for Pancreatic NETs - 1

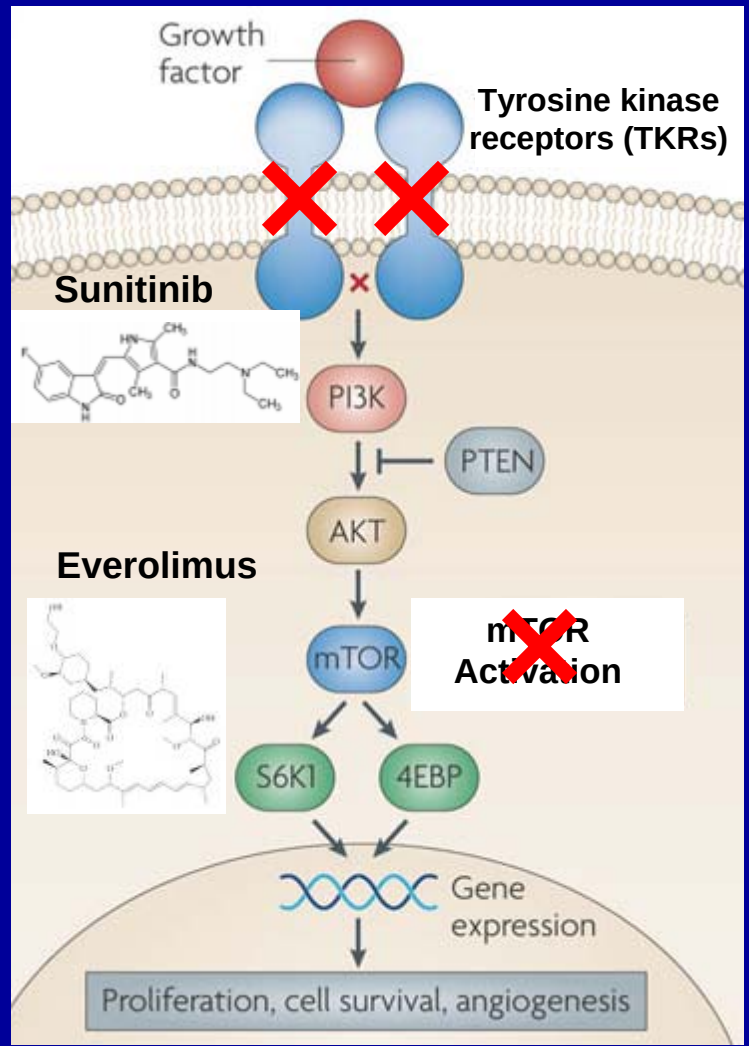
- **Pancreatic NETs express:**
  - **Tyrosine kinase receptors (TKRs) including Vascular Endothelial Growth Factor Receptor (VEGF-R) and platelet-derived growth factor receptor (PDGFR)**
  - **Tyrosine kinase receptor mediated and autocrine activation of the mammalian target of rapamycin (mTOR) signalling pathway**



Atkins et al, *Nature Reviews Drug Discovery* 2009

Emerging Treatments for Pancreatic NETs - 2

- Tyrosine kinase receptor (TKR) inhibitors e.g. Sunitinib treatment increased overall survival and doubling in progression-free survival when compared to placebo (11.4 months verses 5 months, *P*<0.001)
- Inhibitor of mTOR pathway, e.g. Everolimus, treatment lead to doubling in the median progression-free survival when compared to placebo (11.0 months versus 4.6 months, *P*<0.001)



Yao *et al. N Engl J Med* 2011
Raymond *et al. N Engl J Med* 2011

Treatment of Pituitary Tumours

DRUGS:

- **Dopamine agonists (cabergoline or bromocriptine) for prolactinomas**

- **Somatostatin analogues / octreotide or lanreotide for somatotrophinomas**

SURGERY:

- **Transphenodal surgical selective hypophysectomy**

RADIOTHERAPY:

- **Reserved for residual unresectable tumour tissue**

Treatment of MEN1 Tumours

Thymic, Bronochopulmonary and Gastric NETS

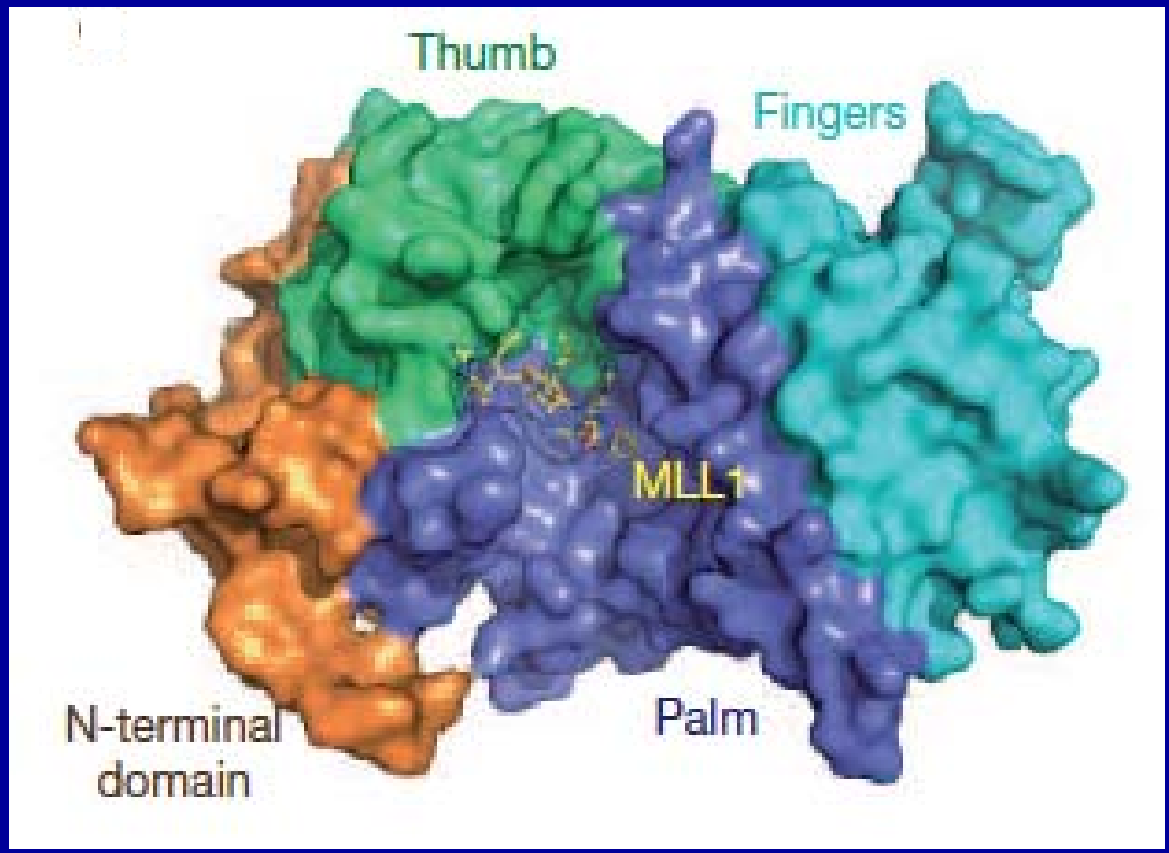
- **Surgery (curative) whenever possible**
- **Somatostatin analogues, radiotherapy, chemotherapy for advanced disease**

Adrenal tmours

- **Surgery for functioning tumours (e.g. hyperaldosteronism or hypercorticolism), and non-functioning tumours in >4cm in size, or with significant growth over a 6 month interval**

Emerging Possible Treatments for MEN1

Crystal structure of Human Menin reveals it to have a 'left hand structure' with a deep pocket, in which MLL1 (mixed lineage leukaemia protein 1) interacts



Nature (2012) 482: 542

High-throughput screening of compounds has identified that Thienopyrimidine (TPyr) targets Menin and suppresses MLL, and second-generation analogues of Tpyr bind to wild-type Menin but not Menin-mutants that involve interaction site with MLL

Nat Rev Drug (2012) 11: 190;
Nat Chem Biol (2012) 8: 277

Summary

- Advances in the treatment for MEN1 tumours are emerging
- Patients and their families should be managed by a multi-disciplinary team (MDT) consisting of relevant specialists with experience in management of MEN1
- MDT representation should include physicians (endocrinologists, gastroenterologists and oncologists), endocrine surgeons, histopathologists, radiologists and clinical geneticists

New Treatments for Non-Functioning Pancreatic NETS

- **Tyrosine kinase receptor (TKR) inhibitors**

  Sunitimib led to increased overall survival and a doubling in progression-free survival when compared to placebo treatment (11.4 v 5.5 months, p<0.001) (2 of the 171 patients had MEN1)

  NEJM (2011) 364: 301

- **Mammalian target of rapamycin (mTOR) inhibitors**

  Everolimus, lead to increased overall survival and a doubling in progression-free survival when compared to placebo treatment (11.0 v 4.6 months, p<0.001) (number of MEN1 patients among the 410 patients, not known)

  NEJM (2011) 364: 514

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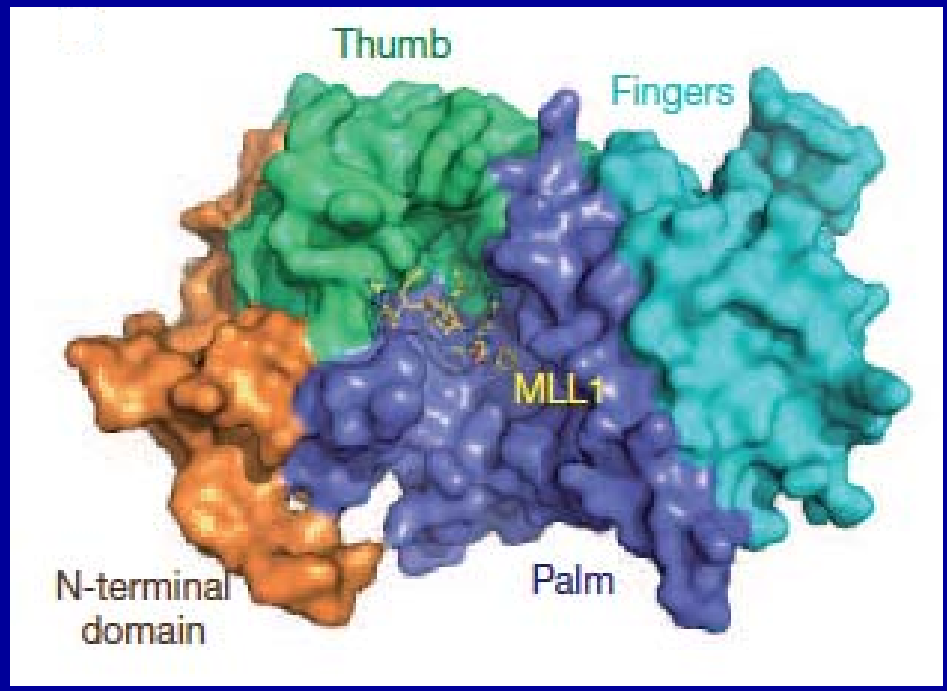

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