

Neuroendocrine tumours – improving treatment through clinical trials

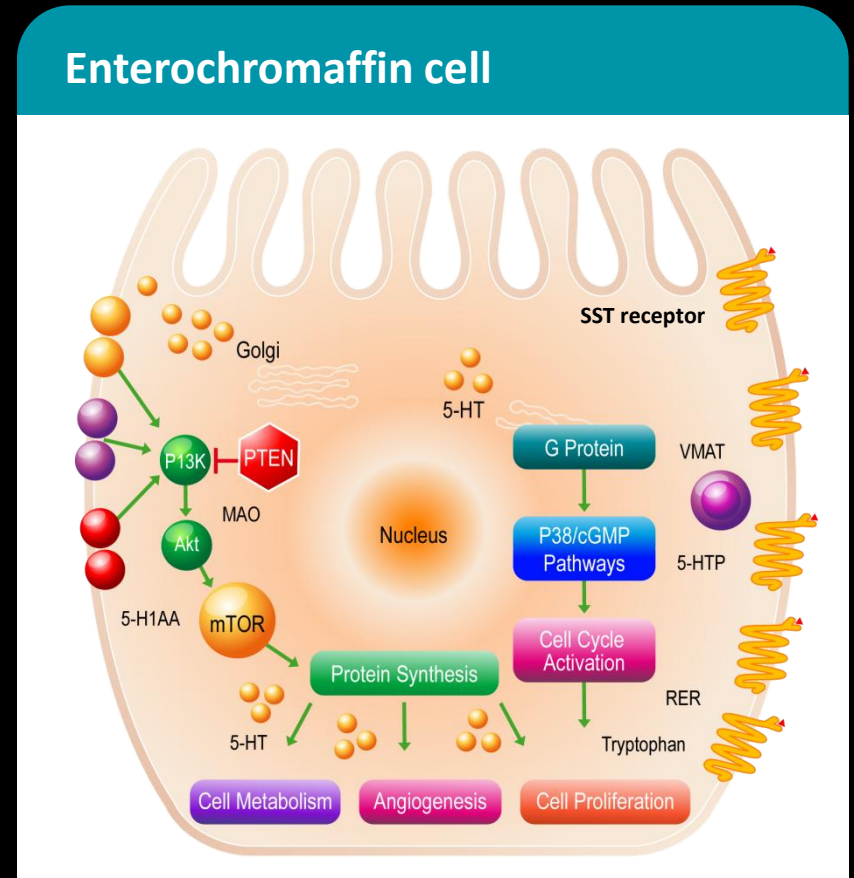
- Dr Pippa Corrie
- Consultant Medical Oncologist
- Cambridge University Hospitals NHS Foundation Trust

Neuroendocrine tumours – improving treatment through clinical trials

- NETs: a clinical challenge
- Some background facts
- Impact of new treatments
- Benefits of clinical trials

NETs: a clinical challenge

- NETs arise from enterochromaffin cells in neuroendocrine tissue
- The term NETs covers a diverse group of malignancies
- May be functioning or non-functioning



History of NETs

- NETs have been recognised as a distinct group of tumours since the late 19th century
- The clinical features of carcinoids were first described in the early 20th century
- Over the past 60 years, significant advances have been made in the diagnosis and treatment of NETs

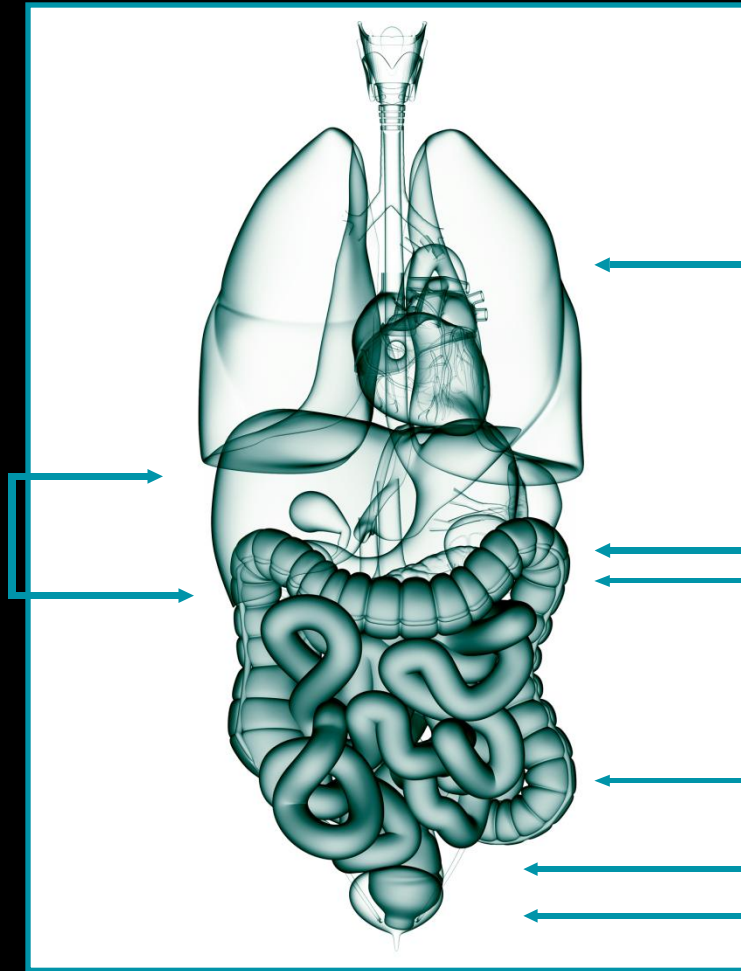
Overview of NETs

- Rare cancer that develops from hormone-secreting cells¹
- NETs are sometimes called carcinoid tumours¹
 - Can be both symptomatic and asymptomatic
 - May be undetected for years without obvious signs or symptoms
- May produce peptides that cause characteristic syndromes²
- Classified according to embryonic origin³
- The majority of NETs are found in the GI tract⁴

NET Classification according to Embryonic Origin

Pancreatic NETs

- Insulinoma
- Glucagonoma
- VIPoma
- Somatostatinoma



Other NETs

Foregut

- Bronchi
- Gall bladder
- Stomach
- Duodenum

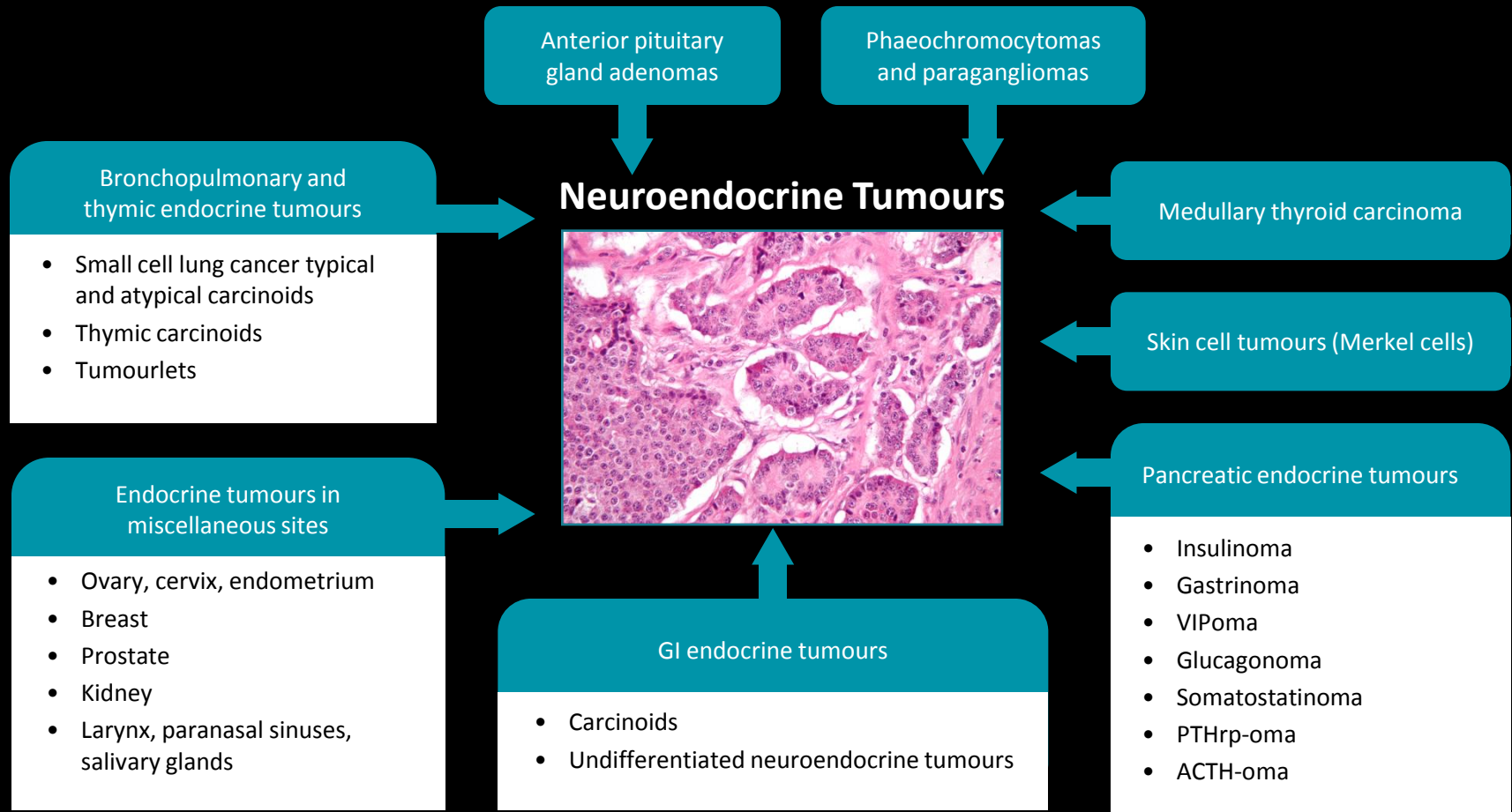
Midgut

- Appendix
- Ileum
- Jejunum
- Right colon

Hindgut

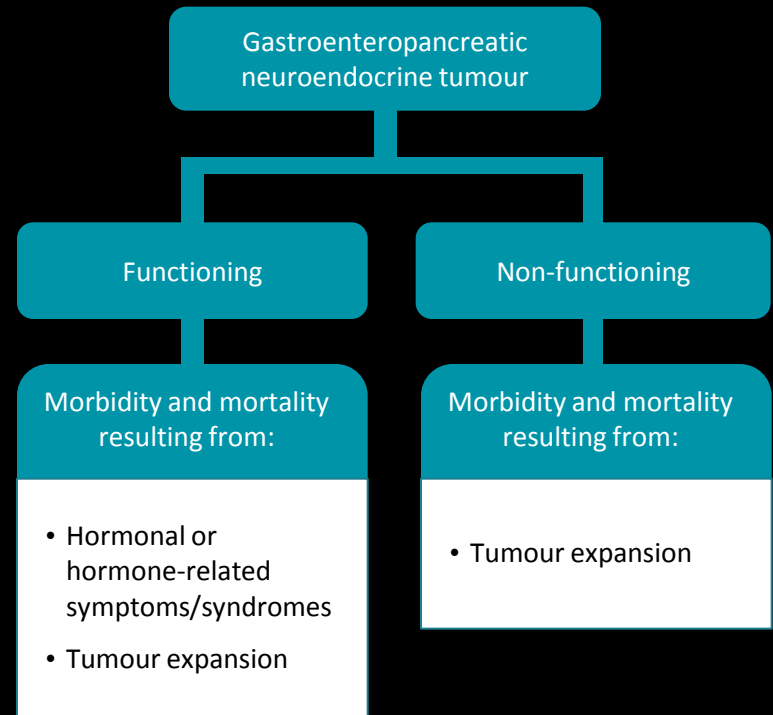
- Left colon
- Rectum

Types of NET



Functioning vs. Non-Functioning GEP-NETs

- Functioning tumours release hormones that induce clinical syndromes¹
 - Also known as symptomatic NETs
 - Carcinoid tumours are the most common type of functioning GEP-NET²
- Non-functioning tumours have no syndrome associated with hormone release¹



Incidence of NETs

- ~ 3,000 cases of NETs are diagnosed each year in the UK¹
- Incidence is around 3 per 100,000 in the UK, with a slight predominance in women²
 - Incidence under recognised¹
 - Median age at diagnosis >50 years³
- GEP NETS represent about 2% of all GI tumours⁴

1. NET Patient Foundation. Available online at: <http://www.netpatientfoundation.com/?cat=97>. Accessed August 2009.

2. Ramage JK *et al.* *Gut* 2005; 54(Suppl IV): IV1–IV16.

3. Yao JC *et al.* *J Clin Oncol* 2008; 26(18): 3063–3072.

4. Massironi S *et al.* *World J Gastroenterol* 2008; 14: 5377–5384.

Incidence of NETs: UK

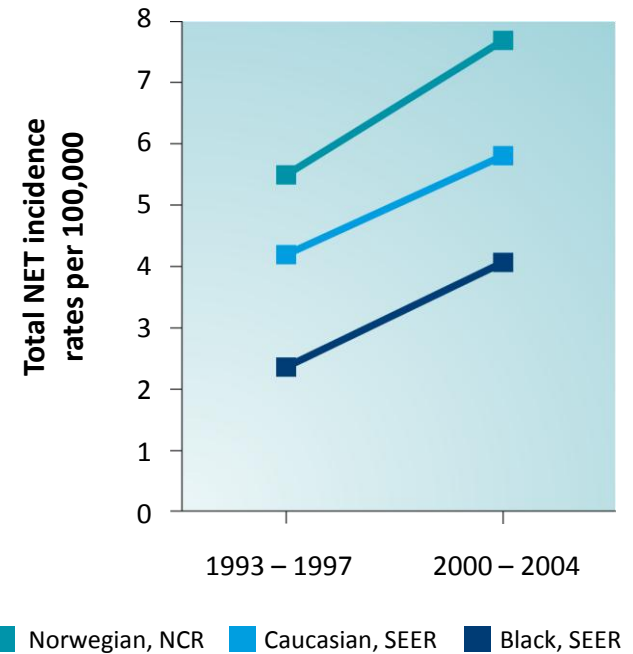
Expected number of NETs per year based on an estimated UK population of 60 million

Tumour type	Incidence	Expected number
Non-functioning	50/million	3000
Carcinoid	20/million	1200
Insulinoma	1–2/million	60–120
Gastrinoma	1–2/million	60–120
VIPoma	1/10 million	6
Glucagonoma	1/10 million	6
Somatostatinoma	1/10 million	<6

Incidence of NETs: US and Europe

- Increasing incidence is illustrated by two large NET databases:¹
 - Surveillance, Epidemiology and End Results (SEER) programme, US
 - Norwegian Registry of Cancer (NCR)
- Reasons for increase could include:
 - Improved diagnostic techniques^{1,2}
 - Increased awareness/more frequent cancer screening^{1,2}
 - Environmental factors¹

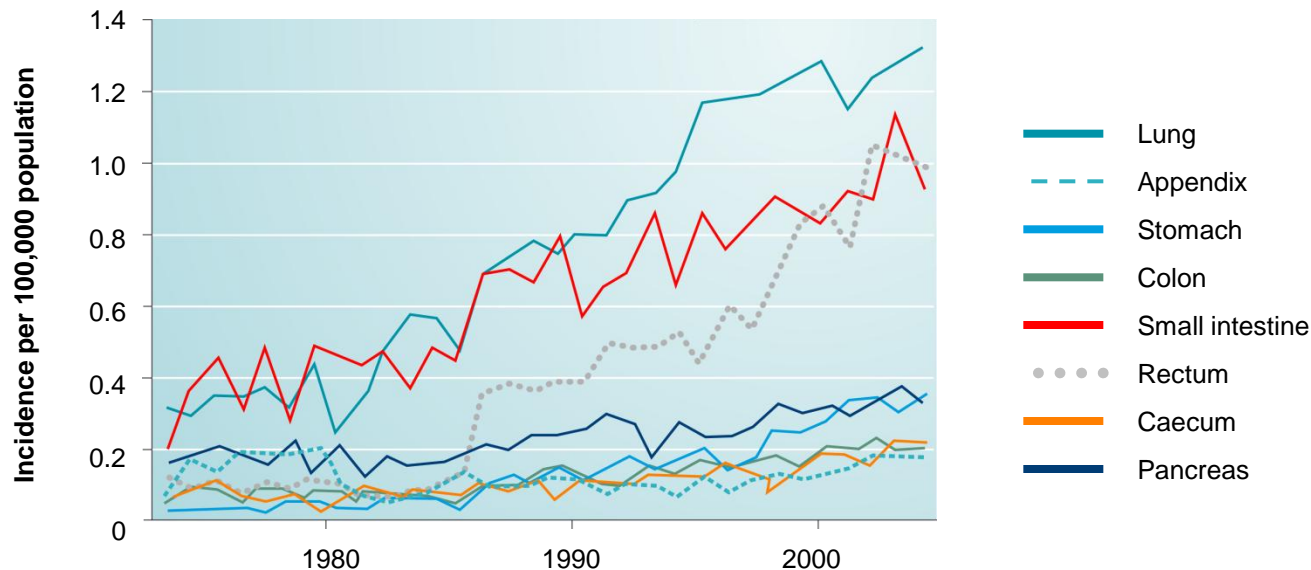
Increase in NET incidence over the past decade



Incidence of NETs: US

- Incidence of NETs has increased dramatically
- 5-fold increase in NETs incidence in past 30 years

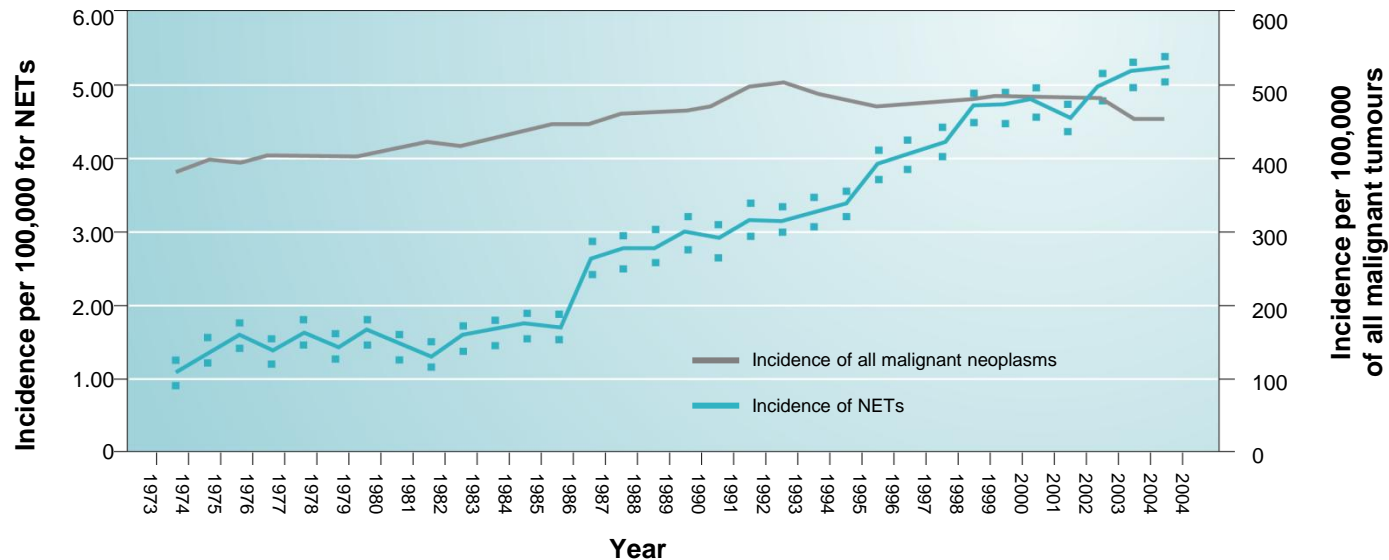
Increase in incidence of NETs for all primary sites: US data



Incidence of NETs versus other Malignancies

- According to US data, the incidence of NETs has been increasing over the past 30 years

The incidence of NETs is now higher than other malignant neoplasms: US data



Treatment options

- Surgery
- Local treatments
 - Local ablation techniques
- Radiotherapy
- Systemic therapy ('chemotherapy')
 - Cytotoxic chemotherapy
 - Immunotherapy
 - Biological agents

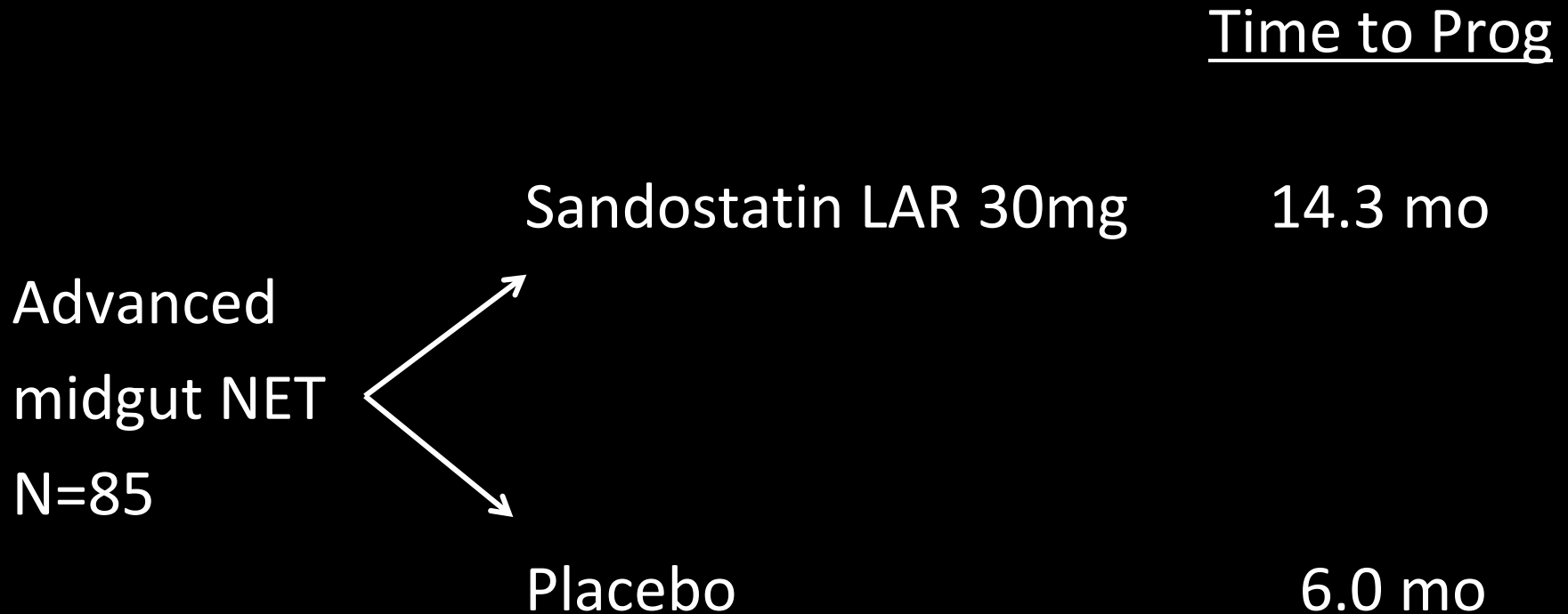
Role of conventional chemotherapy

- Pancreatic and other foregut NETs appear to respond to cytotoxic chemotherapy
- Streptozocin + 5fluorouracil
- Streptozocin + doxorubicin
- Streptozocin + capecitabine
- Streptozocin + capecitabine + cisplatin
- Cisplatin + etoposide
- Temozolamide

Role of biological therapy

- Hormones: somatostatin analogues
- Sunitinib
- Everolimus

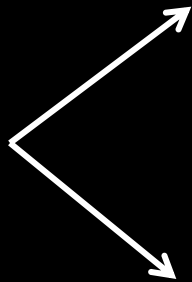
PROMID study



Pfizer study

Prog-free survival

Advanced
pancreatic
NET



Sunitinib 37.5 mg

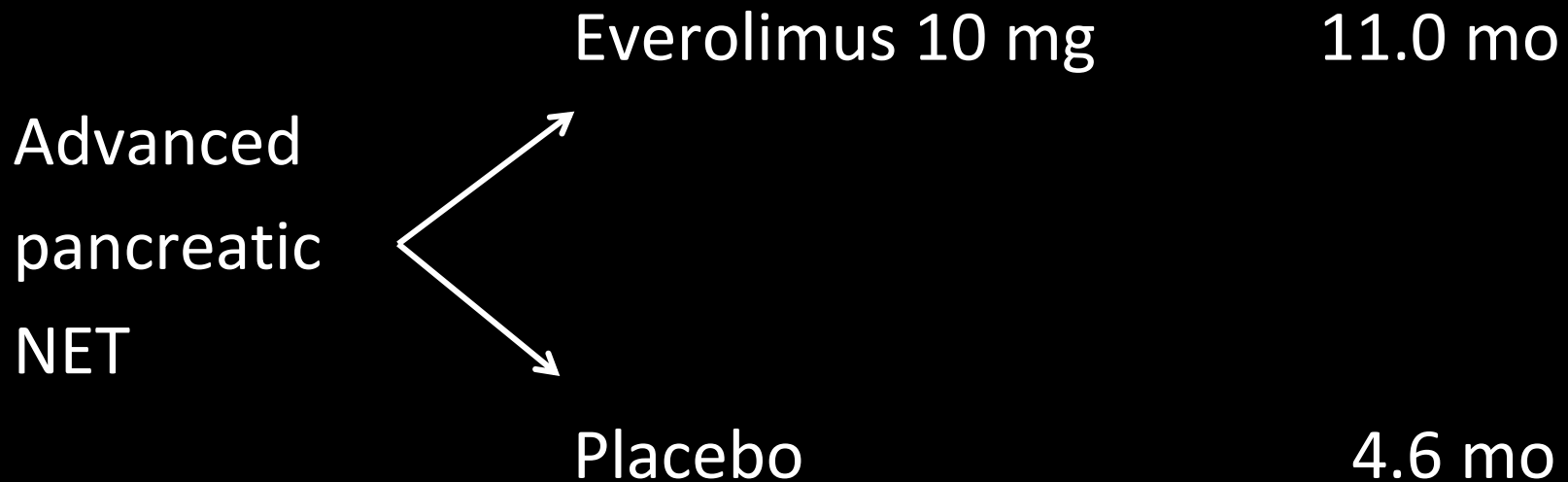
11.4 mo

Placebo

5.5 mo

RADIANT-3 trial

Prog-free survival



RADIANT-2 trial

Prog-free survival

Secretory GI/lung NET	Everolimus 10 mg + octreotide LAR 30mg	16.4 mo
	Placebo + octreotide LAR 30mg	11.3 mo

What do these trials tell us?

- GI NETs:
 - SSAs may slow progression aswell as control symptoms (licensed for both indications)
 - Everolimus may slow progression (not yet licensed)
- Pancreatic NETs:
 - Sunitinib may slow progression (licensed and available to patients via CDF)
 - Everolimus may slow progression (not yet licensed)

Down sides of treatment: drugs have side effects

- SSAs:
 - abdominal pain, diarrhoea, nausea, gall stones
- Sunitinib:
 - Skin rash, hand-foot syndrome, fatigues, high blood pressure, abdominal pain, diarrhoea, anaemia, thrombocytopaenia, neutropaenia
- Everolimus:
 - Sore mouth, skin rash, diarrhoea, fatigue, infections, anaemia, hyperglycaemia

Should all patients receive these drugs?

- Some NETs can remain stable for many months – many years without any treatment at all
- Drugs have side effects which can reduce quality of life
- New drugs are very expensive
 - Approx £1,000 - £3,500 per month

Role of clinical trials

- Clinical trials generate the evidence needed to show that a new treatment works
- Based upon a scientific hypothesis, which needs testing in real life
- Test safety, toxicity, benefits
 - quantity of life, quality of life, comparisons with current standard of care, financial aspects

Clinical trials – challenges for patients

- Dealing with uncertainty
 - Comparing 2 or more treatments
 - Randomisation
 - Placebos
- May involve additional interventions
- New treatments can sometimes harm rather than help
- Feeling of being a 'guinea pig'
 - Others might benefit, but what's in it for me?

Clinical trials – patient benefits

- Access to state of the art treatment
- Close contact with specialist team
- Close monitoring
- Improved quality of care
- Improved sense of well being
- In some cases, improved chance of therapeutic benefit

Clinical trials – patient benefits

Clinical trials



More effective treatments



Improve patient outcomes

SUMMARY

- NETs are a very mixed group of cancers
- Outcomes vary widely from curable to life-threatening
- Incidence of NETs is increasing
- New treatments tested in clinical trials have been shown to improve disease control and progression-free survival

Any Questions?

