Update on systemic treatment with particular focus on bone metastases

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Introduction

Aim

- To clarify how we define a neuroendocrine tumour
- To outline the use of systemic therapies including tablets, chemotherapy, and long acting octreotide
- To describe the treatment of bone metastases as an example

Please feel free to ask any questions as we go along

What is a neuroendocrine tumour (NET)?

A NET is a tumour which displays neuroendocrine features when the pathologist looks at the cells down a microscope.

These can arise anywhere in the body but commonly start in the pancreas, bowel (small or large) and lung.

They are a very variable group of tumours, and behave in many different ways. Some grow very slowly, some grow very fast. Some secrete hormones, some don't.

Why are NETs different?

Most oncology is organised by where the cancer started

NETs are different. We have categorised a group of patients depending on what their tumour looks like down the microscope. This is because the we have learnt that NETs share certain important features. But it brings about some challenges:

a) Each patient's tumour must be treated on its individual features because the behaviour varies
b) NETs are rare so doing research is challenging

The use of systemic therapy

Systemic therapies are tablets or injections aimed at reducing the size of all the tumours in the body

They are not strong enough to offer a cure

We offer systemic therapies if

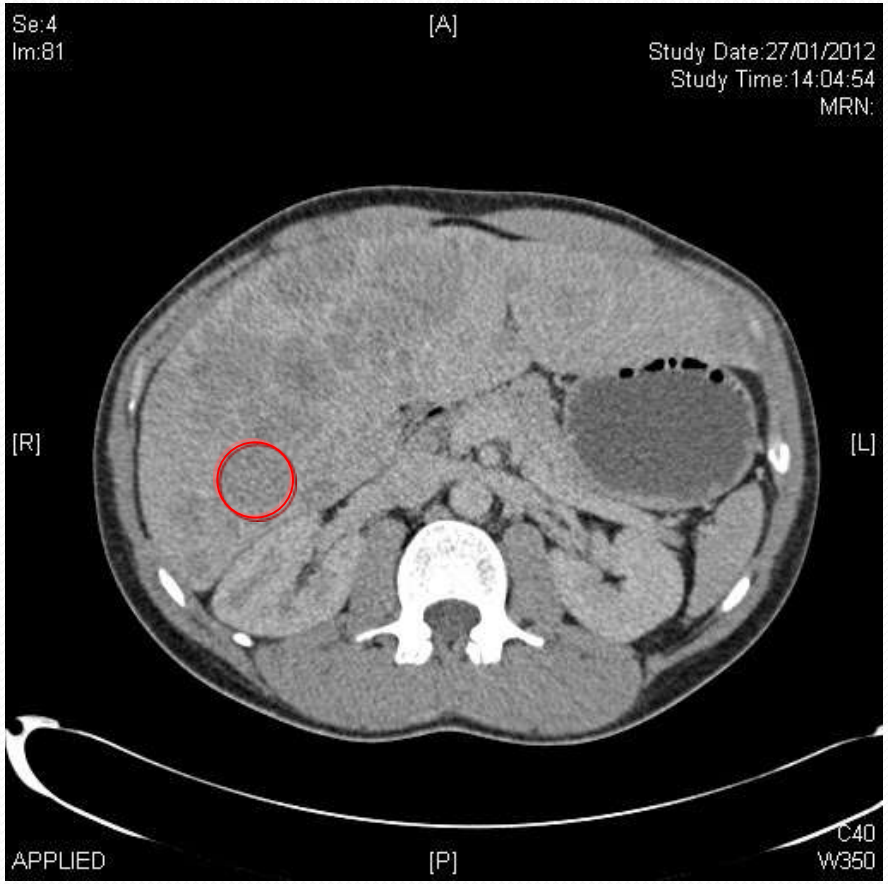
a) local treatment options such as surgery and liver directed therapy are not suitable

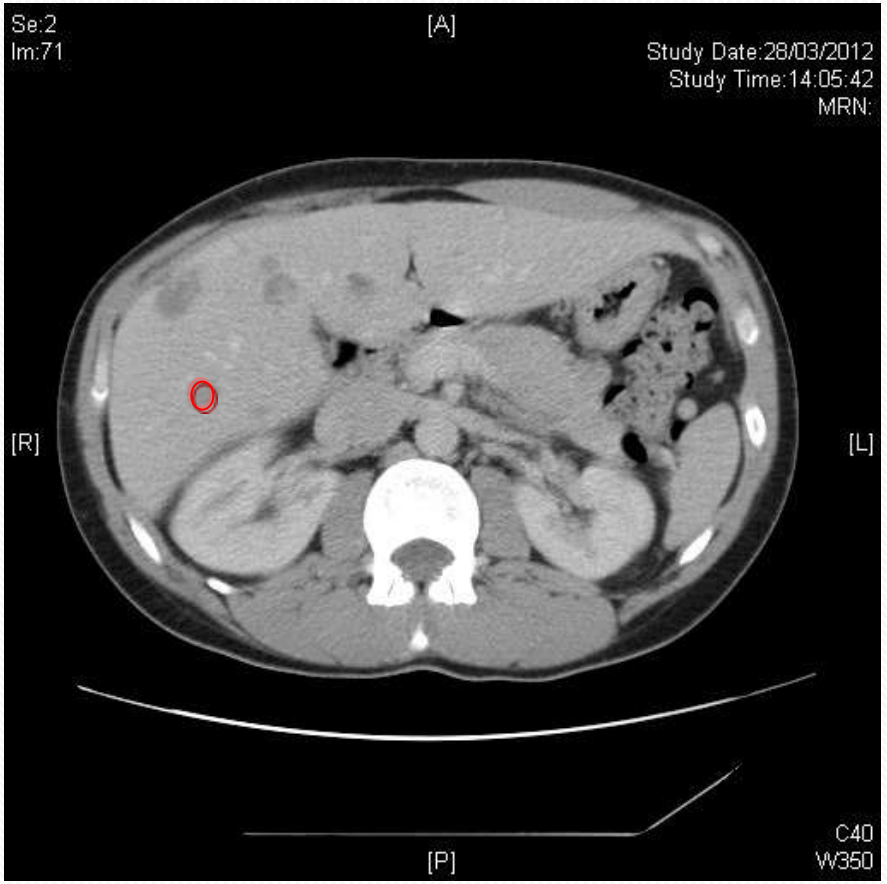
and

b) the potential benefits outweigh the side effects

All treatment is evidence based

The aim of treatment is to shrink the tumours



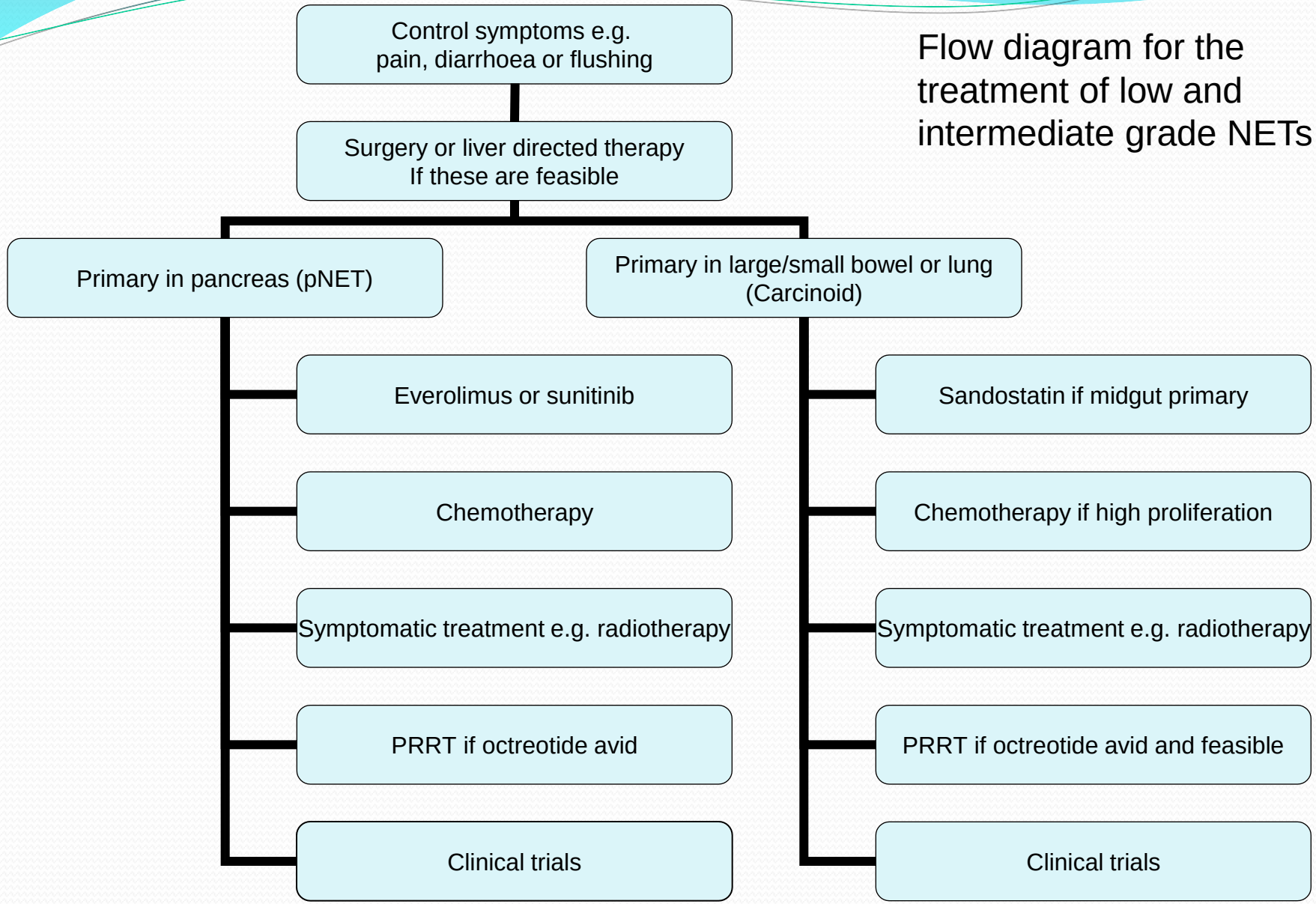


The scan is not the only way to know if the treatment is working

If the tumours are shrinking there will usually be

- Improvement in disease related symptoms
- Reduction in flushing, diarrhoea if carcinoid syndrome is present
- Improvement in organ function if previously compromised

Flow diagram for the treatment of low and intermediate grade NETs



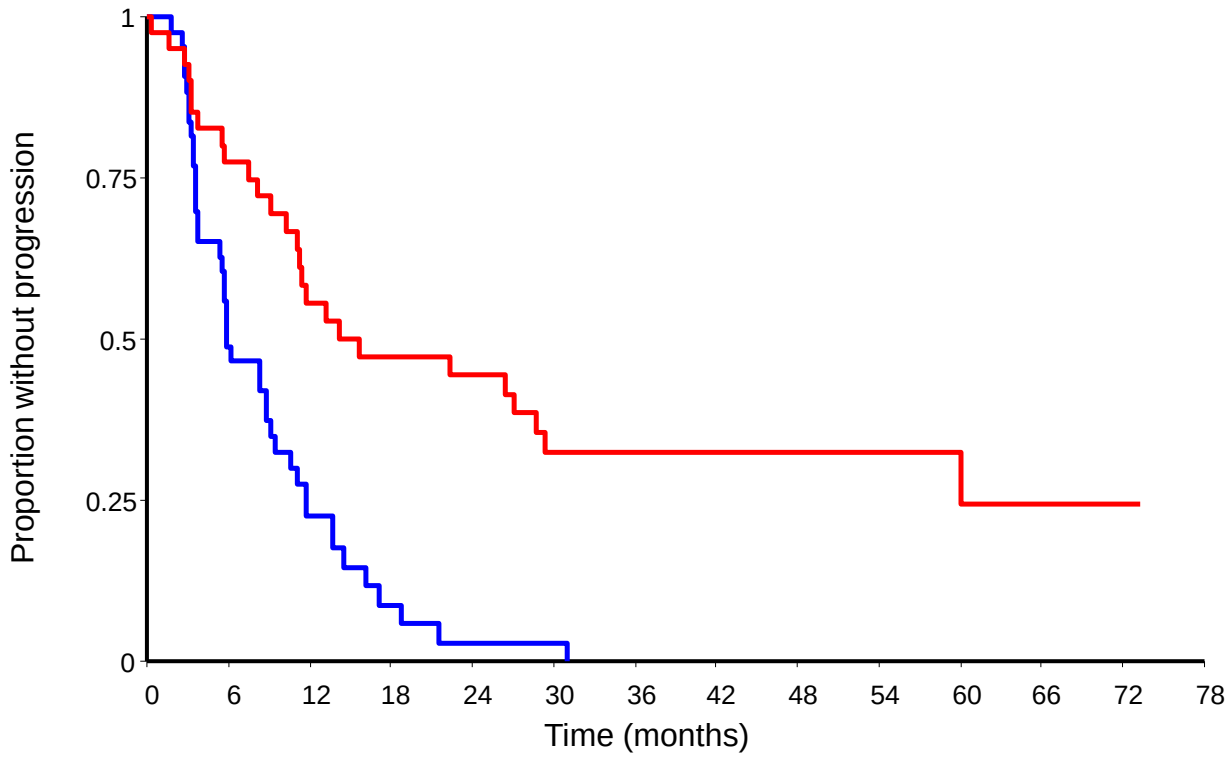
How effective are these treatments?

- Long acting octreotide
- Targeted therapy (everlimus and sunitinib)
- Chemotherapy

PRRT will be covered elsewhere

Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression Compared with Placebo

- 66% reduction in the risk of tumour progression
  HR=0.34; 95% CI: 0.20–0.59; P=0.000072



Octreotide LAR 30 mg: 42 patients / 26 events
Median TTP = 14.3 months [95% CI: 11.0–28.8]

Placebo: 43 patients / 40 events
Median TTP = 6.0 months [95% CI: 3.7–9.4]

Based on the conservative ITT analysis

Rinke A *et al*. *J Clin Oncol* 2009;27:4656–4663

NOVARTIS

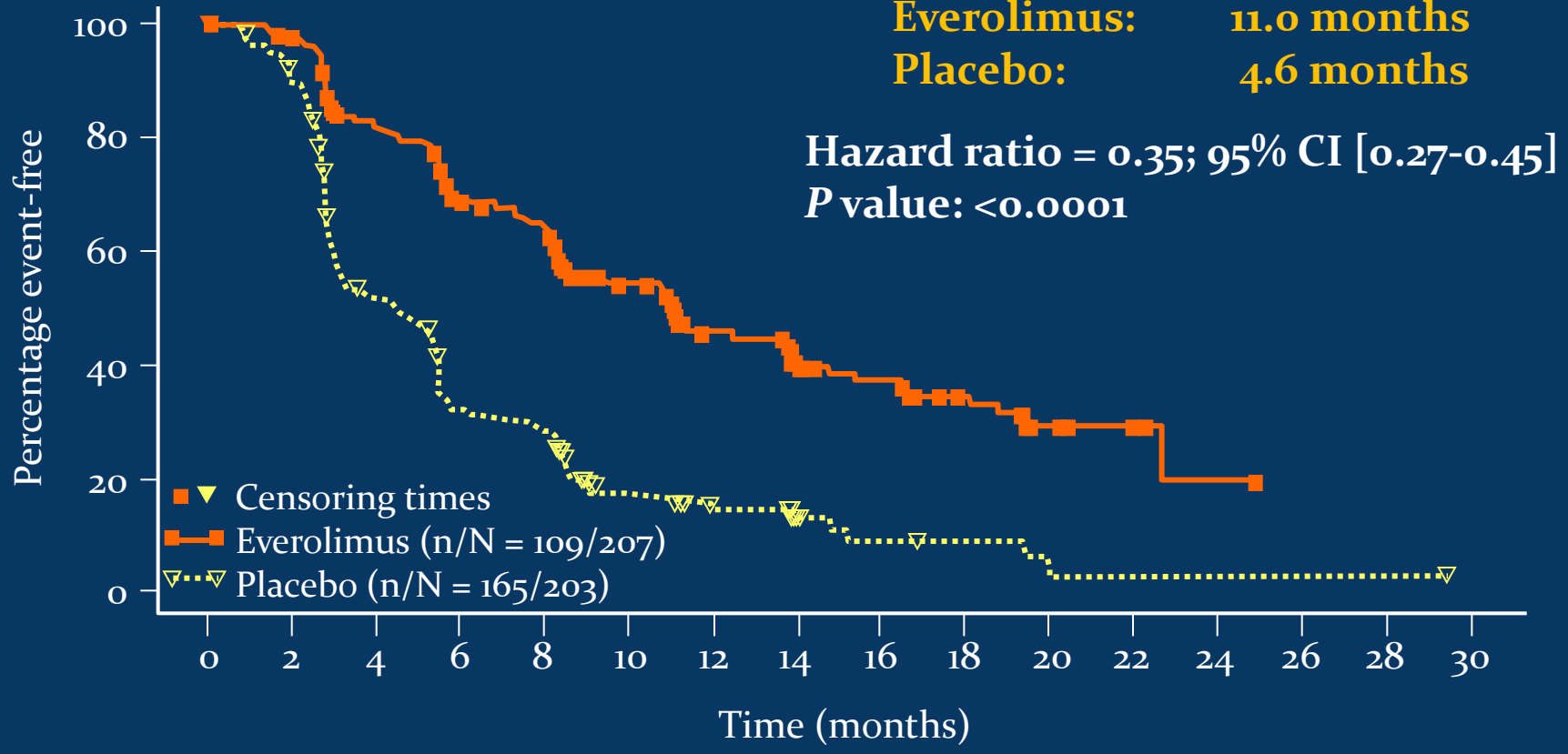
Everolimus and sunitinib

These are targeted agents, working to try to reverse some of the specific features displayed by malignant cells i.e. uncontrolled cell division and angiogenesis (new blood vessels).

They are tablets, and tend to have less side effects than intravenous chemotherapy.

Everolimus targets intracellular signalling, and sunitinib targets new blood vessel formation.

Everolimus: Efficacy Results



Kaplan-Meier Median PFS

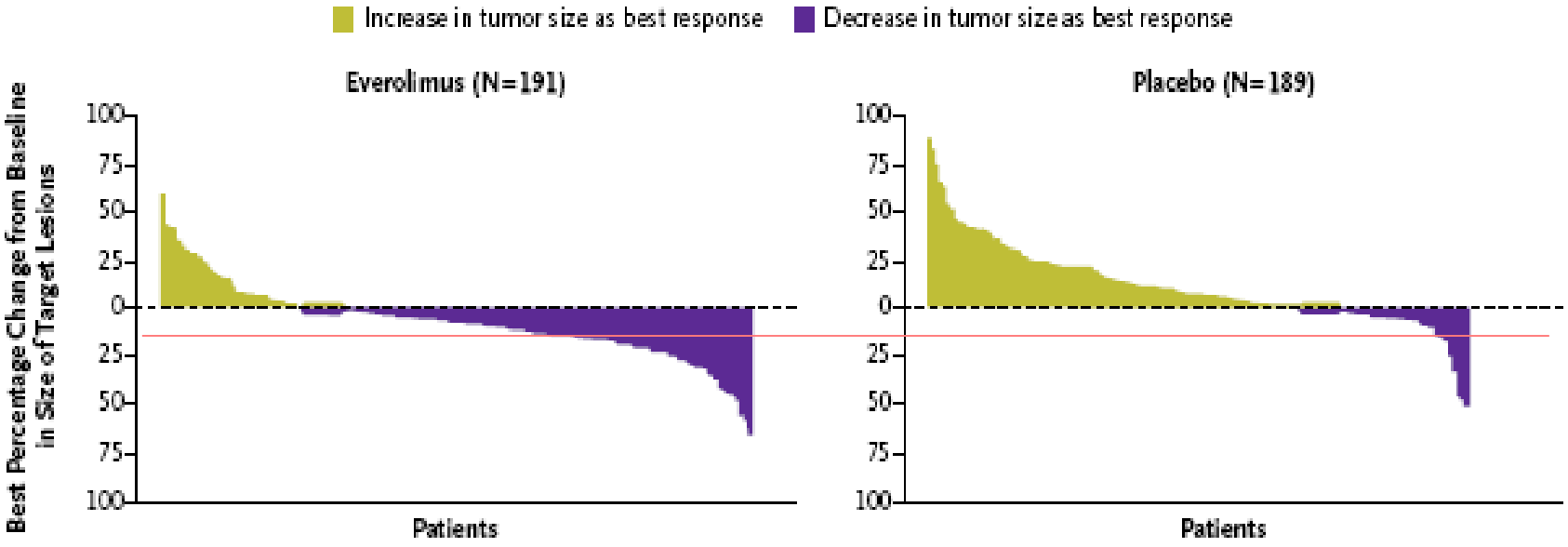
Everolimus: 11.0 months

Placebo: 4.6 months

Hazard ratio = 0.35; 95% CI [0.27-0.45]

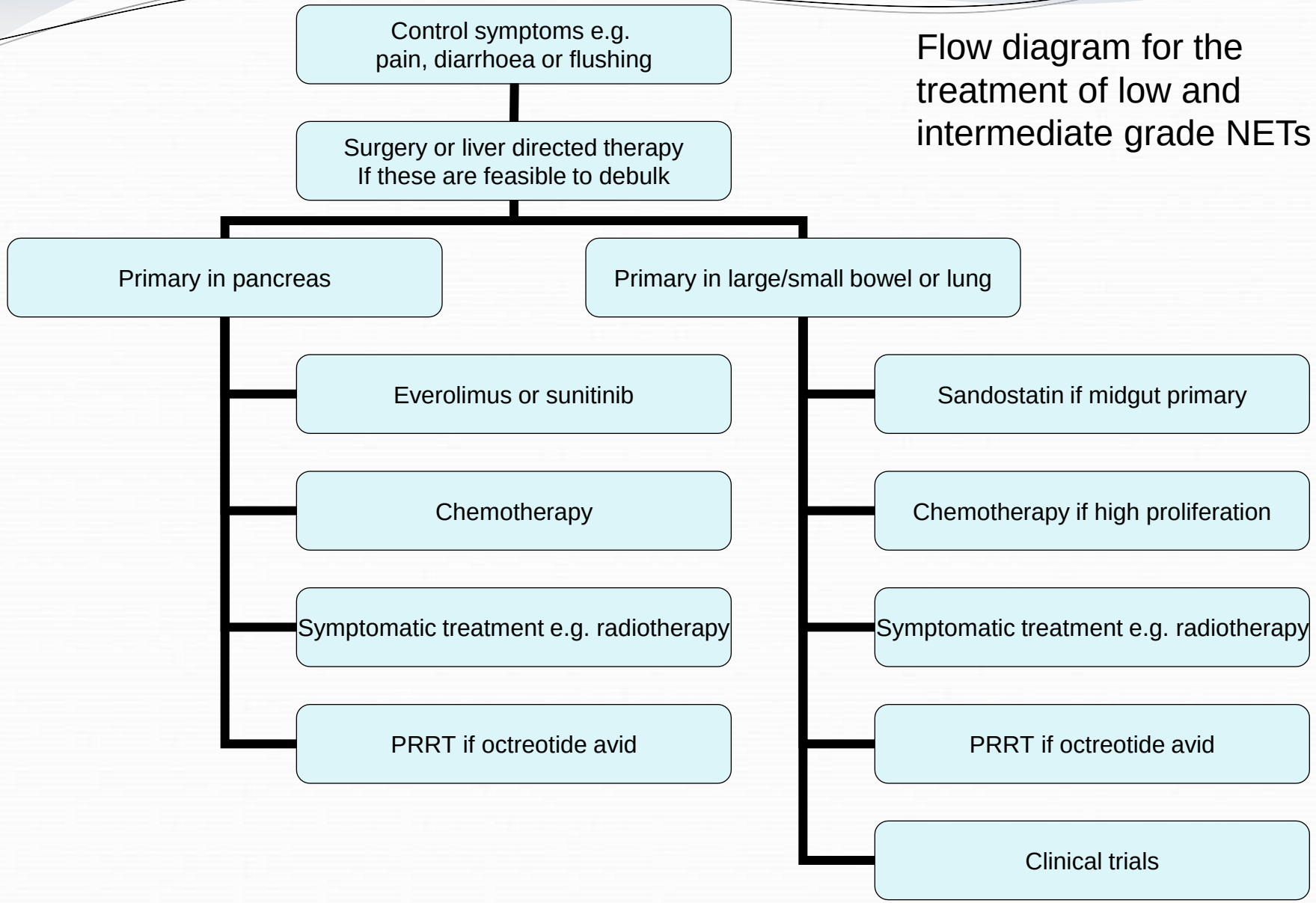
***P* value: <0.0001**

Best Percentage Change from Baseline



	Everolimus *no. (%)*	Placebo
Decrease in size of target lesions from baseline	123 (64.4)	39 (20.6)
No change in size of target lesions from baseline	11 (5.8)	10 (5.3)
Increase in size of target lesions from baseline	43 (22.5)	112 (59.3)

Flow diagram for the treatment of low and intermediate grade NETs



Chemotherapy:efficacy

There have only been 5 randomised trials of chemotherapy regimens, and none compared chemotherapy to placebo.

Cisplatin based chemotherapy is the standard of care for patients with high mitotic rate tumours

Streptozocin based chemotherapy may be offered to patients with low or intermediate mitotic rate tumours

Chemotherapy works better when the primary is/was in the pancreas

FCiSt

FCiSt chemotherapy was developed at the Royal Free

It includes three drugs: 5FU cisplatin and streptozocin

In a series of 79 patients with metastatic or locally advanced NETs the overall response rate was 33%. Stable disease occurred in a further 51%, with progression in 16%. The median time to progression was 9 months.

Can you predict who will benefit?

Patient group		Partial response rate
All		33%
Primary site	Pancreas Elsewhere	38% 25%
Mitotic rate	0-1 2-4 >5	15% 29% 55%

Patient example - presentation

A 72 year old retired nurse, who developed a cough in May 2011. She had smoked for 4 years 40 years ago

Her GP did a routine chest X-ray which showed a small lump in the left lung

This was removed on 2nd Nov 2011. The histology showed a NET of the lung. There was spread to the lymph nodes, and it was an intermediate grade (ki67 15-20%).

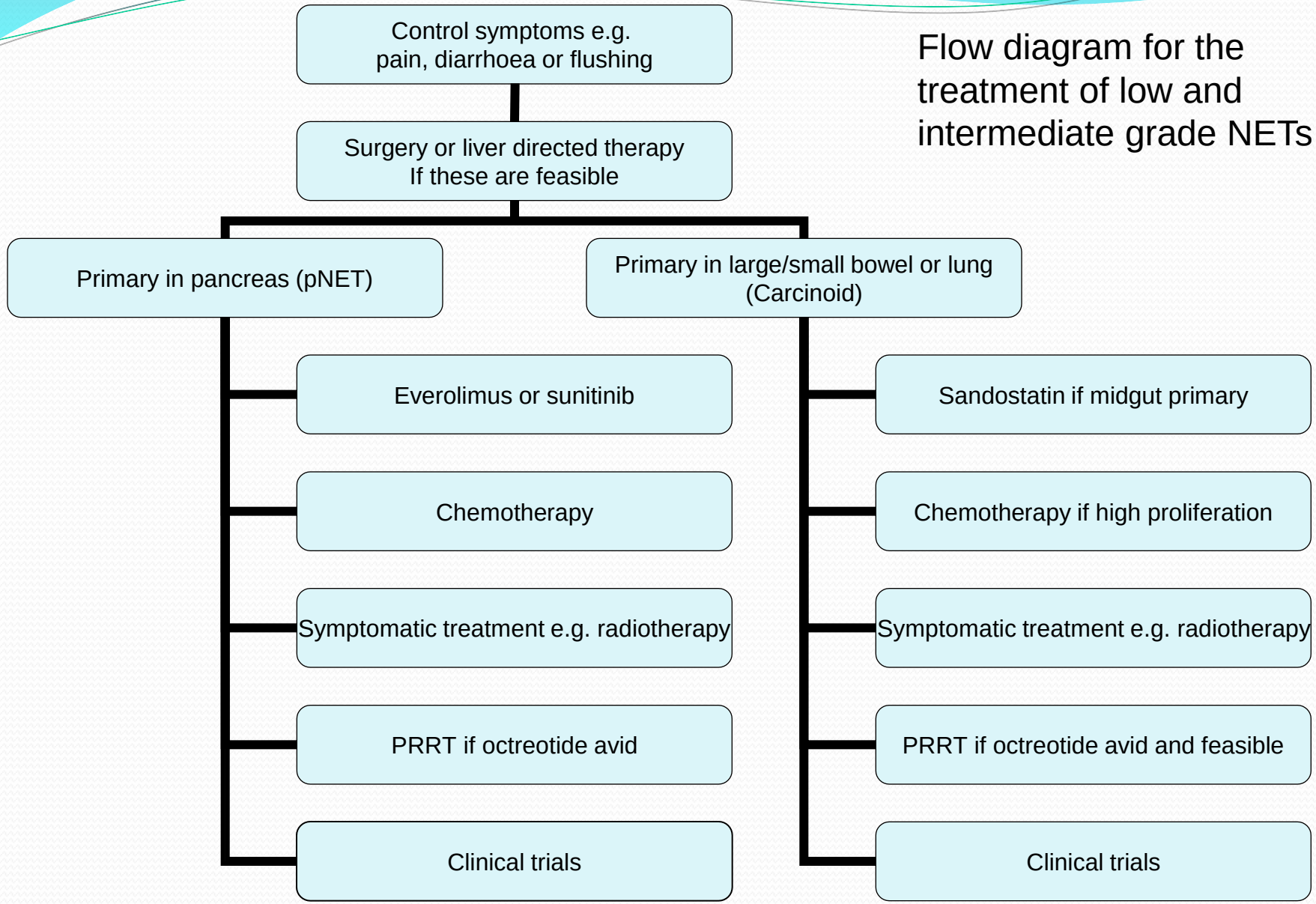
She recovered well, and scans after her operation were all clear.

Patient example - recurrence

Four months after her operation (March 2012) she developed back pain. A bonescan showed the NET had spread to her bones.

A CT scan showed that the only other site of disease were 2 subcutaneous nodules.

Flow diagram for the treatment of low and intermediate grade NETs



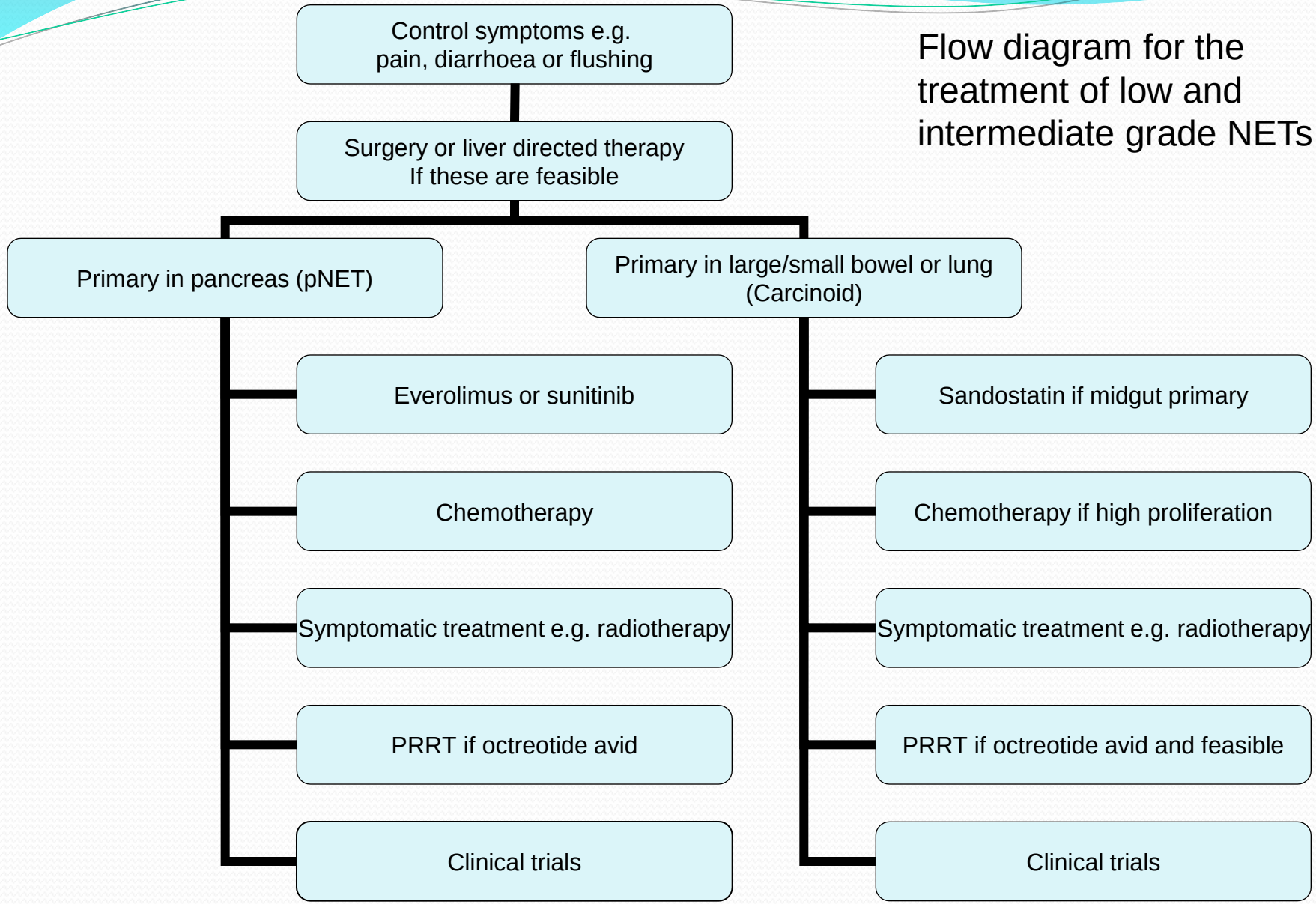
Patient example - progress

The treatment we gave was

1. Resect the biggest subcutaneous nodule
2. Radiotherapy to painful areas (three courses)
3. Pamidronate monthly infusion

This patient was offered chemotherapy, and randomisation into a clinical trial, but she declined both these options. She is currently well, with her pain under control.

Flow diagram for the treatment of low and intermediate grade NETs



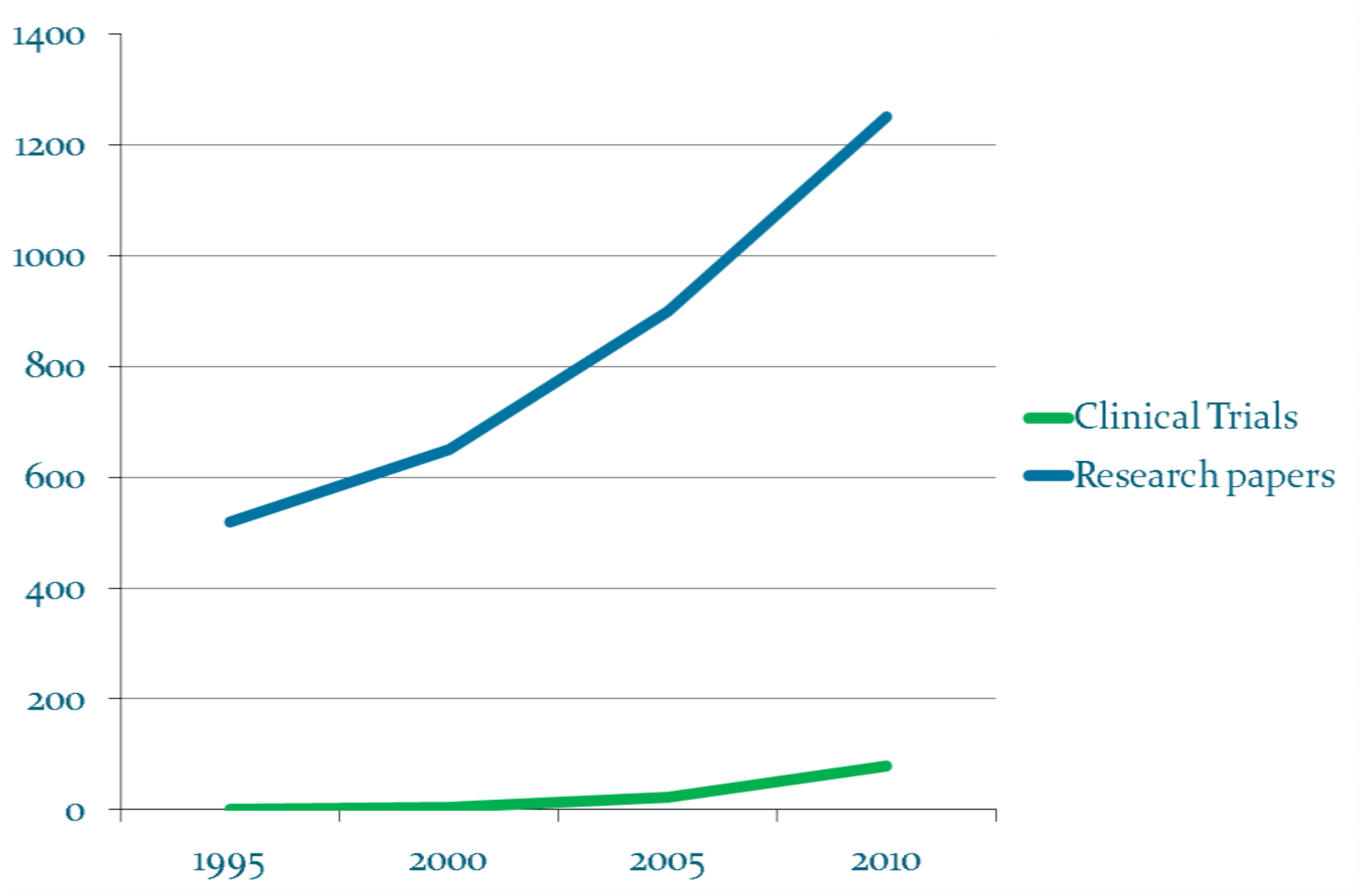
What do we need in the future?

The priority for the care of patients with NET is research.

We need

a) new treatment options
b) better information about the efficacy of current treatments especially chemotherapy
c) to be able to predict how each patients NET will behave

Number of papers and trials about NETs



Kunz P, ASCO 2012

What research are we doing in Southampton?

1. Tumour bank and database
2. Enrolling patients into national and international studies of new treatments
3. Hoping to do some work looking at changes over time in patients who have had multiple surgeries (may be funded by PLANETS).
4. Collaboration with other centres of excellence e.g. UCLH

Summary

Symptom control and surgery are should be considered in all patients with low and intermediate grade NETs

Long acting octreotide helps control symptoms and may also slow disease progression

Chemotherapy can sometimes shrink NETs

There are 2 new targeted agents with good activity available for pancreatic NETs

In the future we hope to discover better ways to select patients who will respond well to chemotherapy, and further exploit the developments in cell biology to treat patients with targeted therapies