Clinical trial endpoints relevant to patients/society for rare tumours

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Disclosure

- Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, Merck Serono, Gilead Science
- Research funding: Sanofi Oncology, Roche, Merck-Serono, Novartis
- Honorarium: Taiho

Consensus Report of the NCI Neuroendocrine tumor Clinical Trials Planning Meeting

- Clinical trials of novel systemic agents for advanced NET
  - Overall survival not a practical endpoint
  - In general, PFS is recommended as the primary end point for phase III studies, as well as for phase II studies where a delay in progression is expected in the absence of significant radiologically defined tumour response

THE ROYAL MARSDEN

Kulke et al J Clin Oncol 2011

EUROPEAN JOURNAL OF CANCER 48 (2012) 385–388

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Current perspective

Poor correlation between progression-free and overall survival in modern clinical trials: Are composite endpoints the answer?

Eitan Amir [a,*], *Bostjan Seruga* [b], *Ryan Kwong* [a], *Ian F. Tannock* [a], *Alberto Ocaña* [a,c]

VOLUME 30 · NUMBER 10 · APRIL 1 2012

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Progression-Free Survival: Meaningful or Simply Measurable?

Christopher M. Booth and Elizabeth A. Eisenhauer, *NCIC Clinical Trials Group, Queen's University, Kingston, Ontario, Canada*

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Correlation of PFS with OS in advanced solid tumours

Tumour primary site	Correlation of PFS to OS
Colorectal Cancer[1]	√
Melanoma[2]	√
Renal cell carcinoma[3]	√
Gliobastoma[4]	√
Locally advanced NSCLC[5]	√
Advanced NSCLC[6]	~
Breast Cancer[7]	×
Gastric Cancer[8]	×
Neuroendocrine tumour	**????**

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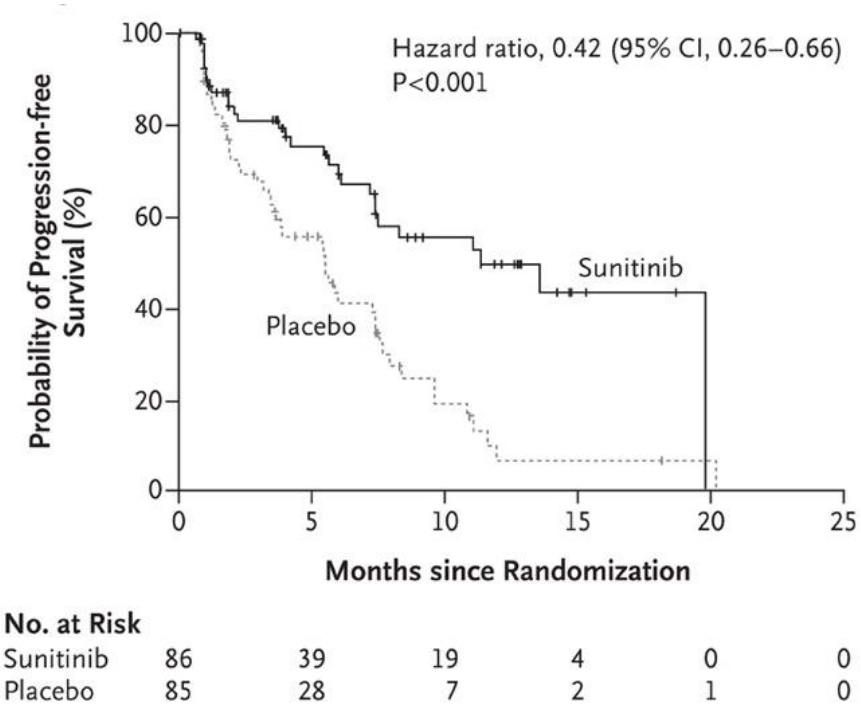
[1]Buyse et al J Clin Oncol 2007; [2]Flaherty et al Lancet Oncol 2014; [3]Halabi et al Cancer 2014; [4]Han et al Neuro Oncol 2013; [5]Mauguen et al Lancet Oncol 2013; [6]Laporte et al BMJ Open 2013 [7]Burzykowski et al J Clin Oncol 2008; [8]Paoletti et al J Natl Cancer Inst 2013

PFS vs. OS

PFS: Sunitinib vs placebo[1]

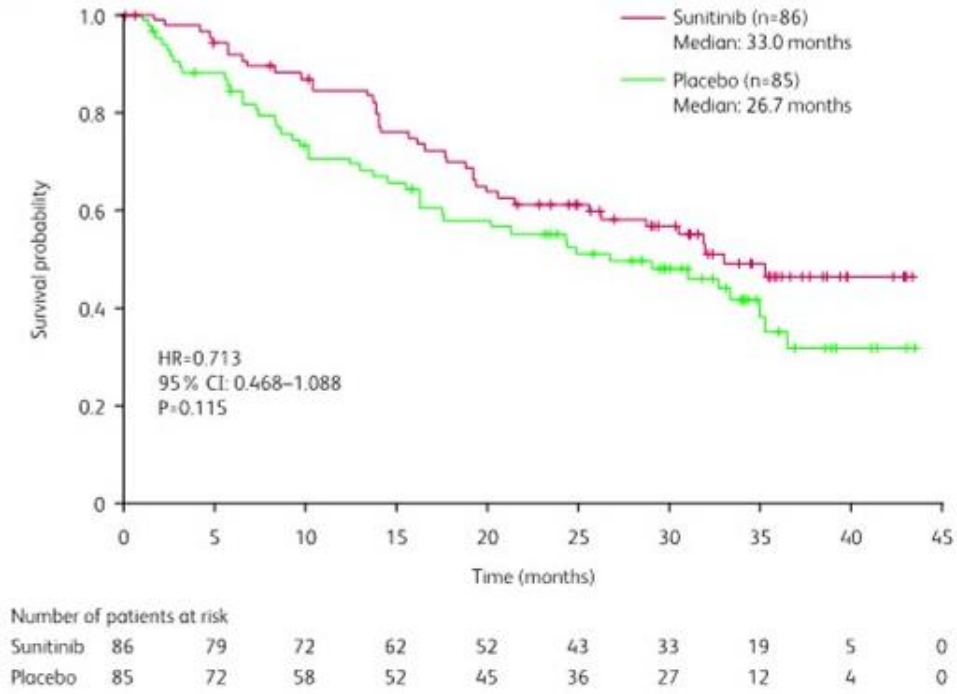


SU PBO

Median PFS 11.4 months 5.5 months

HR: 0.42; 95% CI: 0.26-0.66; p<0.001

OS: Sunitinib vs placebo[2]



SU PBO

Median OS 33 months 26.7 months

HR: 0.71; 95% CI: 0.47-1.09; p=0.11

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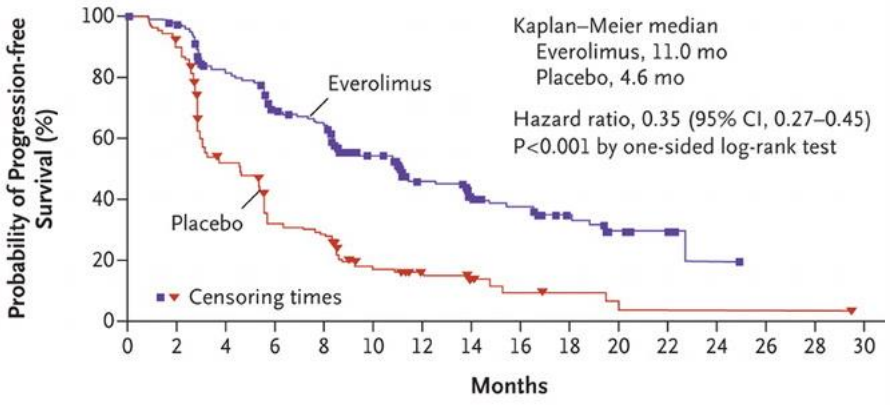
[1]Raymond et al N Engl J Med 2011; [2]Vinik et al ASCO 2012

PFS vs. OS

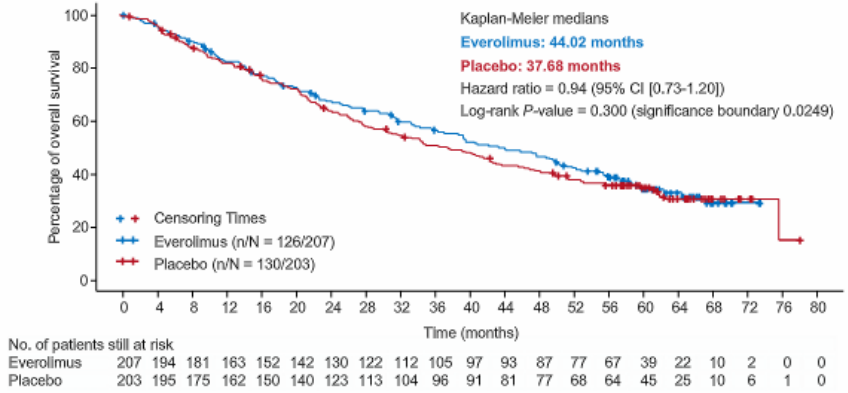
PFS: Everolimus vs placebo[1]



	EVE	PBO
Median PFS	11.0 months	4.6 months

HR: 0.35; 95% CI: 0.27-0.45; p<0.001

OS: Everolimus vs placebo[2]



	EVE	PBO
Median OS	44 months	37.7 months

HR: 0.94; 95% CI: 0.73-1.20; p=0.30

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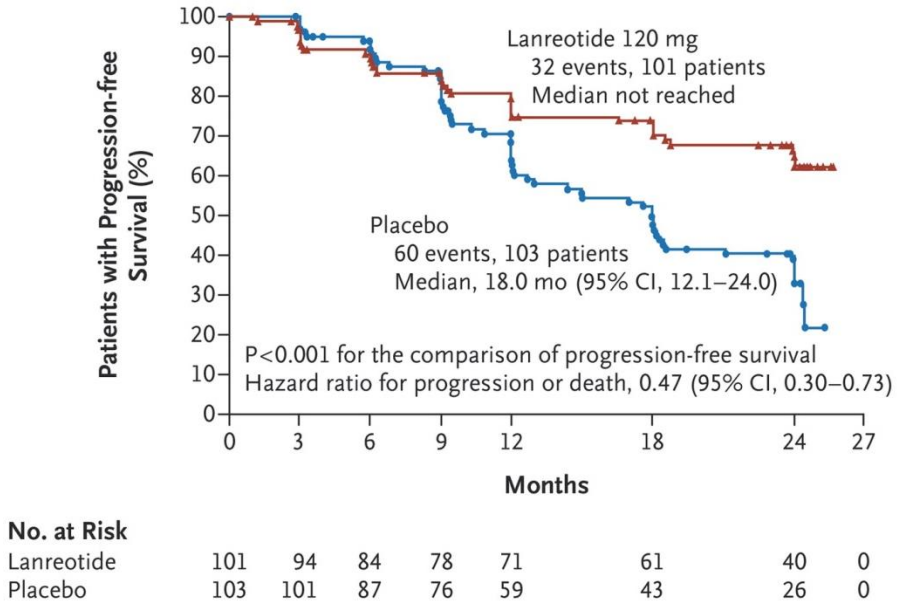
[1]Yao et al N Engl J Med 2011; [2]Yao et al ESMO 2014

PFS vs. OS

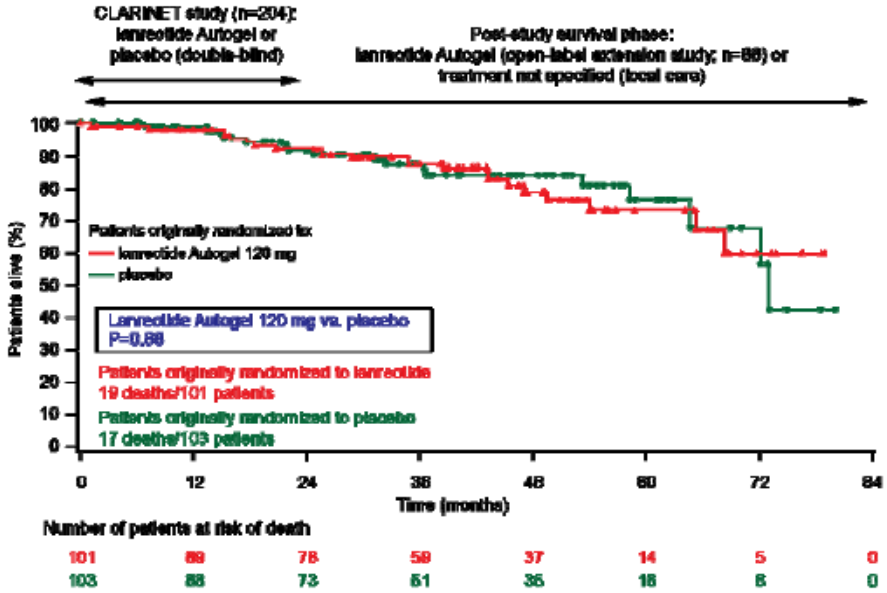
PFS: Lanreotide vs placebo



	LAN	PBO
Median PFS	Not reached	18 months

HR: 0.47; 95% CI: 0.30-0.73; p<0.001

OS: Lanreotide vs placebo



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Caplan et al N Engl J Med 2014

Is there an association between PFS and QoL in solid tumours?

- Only 4 studies assessed this –
  - 1 in colorectal cancer (panitumumab)
  - 2 in breast cancer (lapatinib)
  - 1 in renal cell cancer (pazopanib)
- All reported that being progression free had a statistically significant positive association with better Qol ± ↓disease symptoms
- ?? Publication bias

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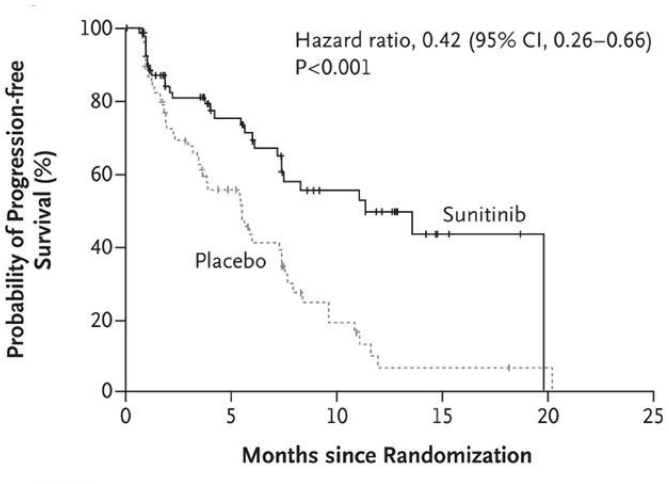
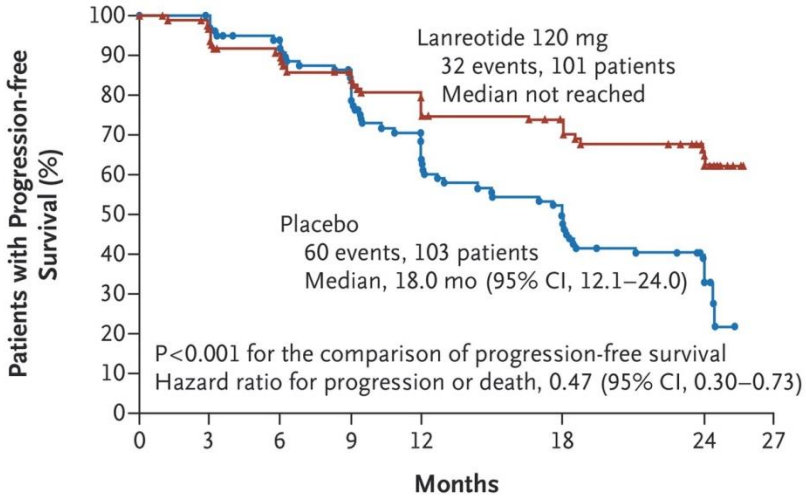
Gutman et al Rockville (MD): Agency for Healthcare Research and Quality (US) 2013

RCTs of neuroendocrine tumours
↑PFS ≠ ↑QoL

Study	n	Treatment arms	QoL instrument	Results
A6181111[1]	144	Sunitinib vs. Placebo	EORTC QLQ c30	Global health status non-significant
CLARINET[2]	204	Lanreotide vs. Placebo	EORTC QLQ c30	Global health status non-significant





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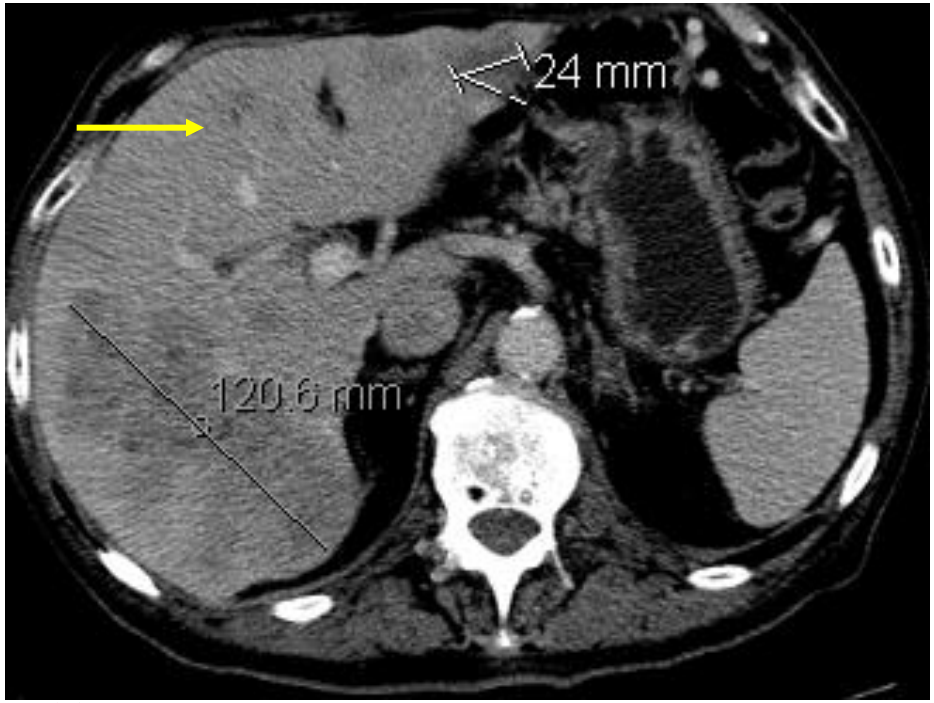
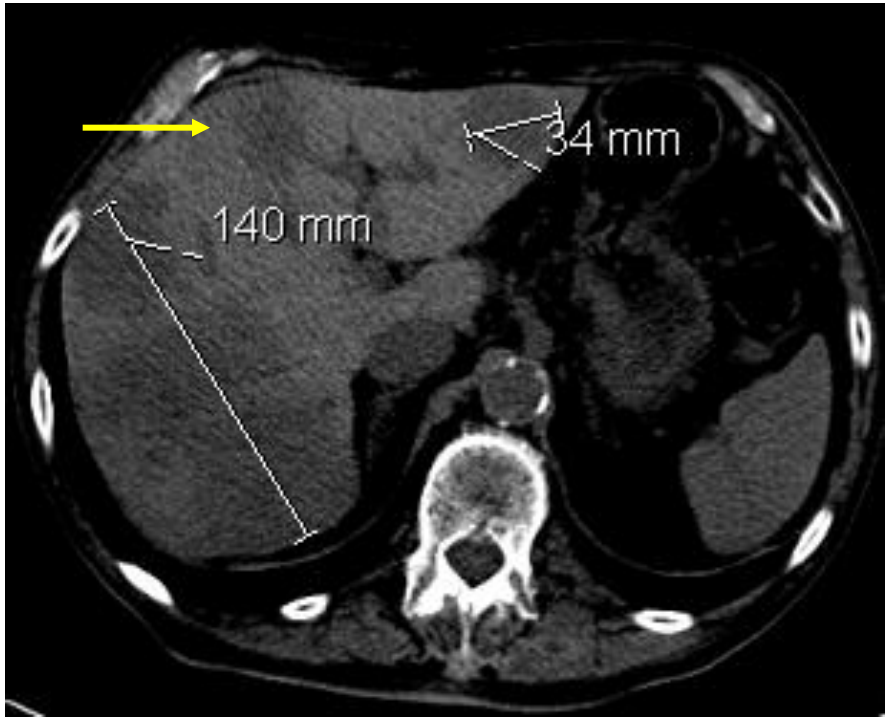
[1]Raymond et al N Engl J Med 2011; [2]Caplan et al N Engl J Med 2014

Pancreatic NET with liver metastases: disease progression but asymptomatic

October 2012



September 2013



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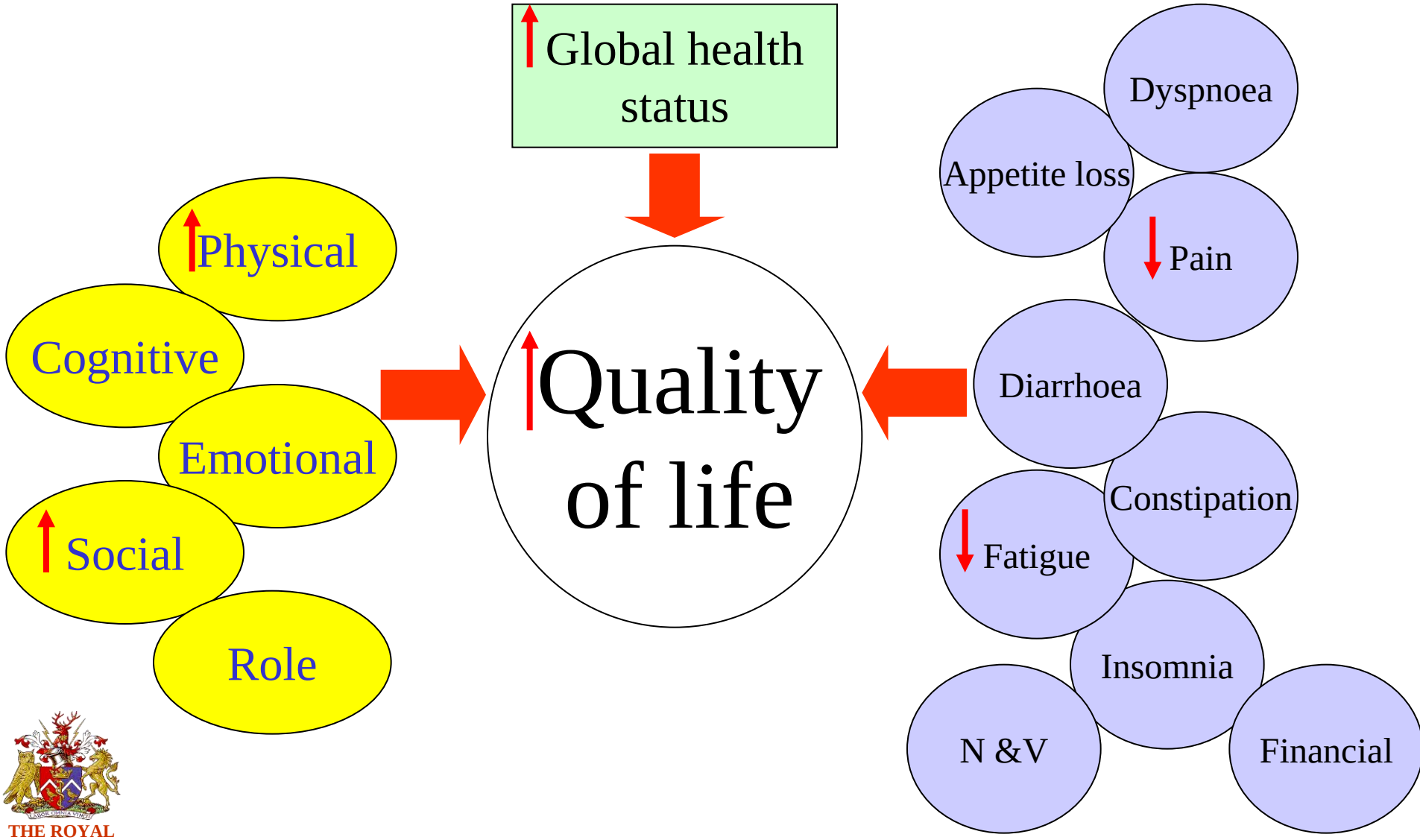
Health related quality of life (QoL) is a multidimensional assessment



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Is QoL different in neuroendocrine tumour (NET) compared to other GI cancer?

- Younger age (median age was 56 in study population)
  - Family, social and financial issues important

- Functioning NETs:
  - Carcinoid – skin flushing, diarrhoea and wheezing
  - Zollinger-Ellison syndrome – GI ulceration, diarrhoea
  - Insulinoma – hypoglycaemia, fits, collapses and sweating
  - Glucagonoma – diabetes and rash
  - VIPoma – severe secretory diarrhoea
  - Somatostatinoma – gallstones, steatorrhoea

- "Rare" disease prompts uncertainty of quality of care

- Studies showed QoL in patients with neuroendocrine tumours significantly worse than general population (at least for Scandinavian), but not consistently so[1-4]

[1]Larsson et al Acta Oncologica 2001; [2]Haugland et al Qual Life Res 2009; [3]Frojd et al Health Qual Life Outcomes 2007; [4]Pezzilli et al World J Gastroenterol 2009

EORTC QLQ – GI.NET 21

	During the past week:		Not at all	A little	Quite a bit	Very much
Endocrine	31. Did you have hot flushes?		1	2	3	4
	32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
	33. Did you have night sweats?		1	2	3	4
Gastrointestinal	34. Did you have abdominal discomfort?		1	2	3	4
	35. Did you have a bloated feeling in your abdomen?		1	2	3	4
	36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
	37. Have you had acid indigestion or heartburn?		1	2	3	4
	38. Have you had difficulties with eating?		1	2	3	4
Treatment related Side effects	39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
	40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
Disease related worries →	41 Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
Social function →	42. Were you concerned about disruption of home life?		1	2	3	4
Disease related worries →	43. Have you worried about your health in the future?		1	2	3	4
Social function →	44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
Weight concern	45. Has weight loss been a problem for you?		1	2	3	4
	46. Has weight gain been a problem for you?		1	2	3	4
Disease related worries →	47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
Pain →	48. Have you had aches or pains in your muscles or bones?		1	2	3	4
Social function →	49. Did you have any limitations in your ability to travel?		1	2	3	4
	During the past four weeks:					
Communication →	50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
Sexuality →	51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

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Davies et al Eur J Cancer 2006

QoL measurement in RCTs of neuroendocrine tumours

Study	n	Treatment arms	QoL instrument	Results
O'toole et al[1]	33	Lanreotide vs. Octreotide	Nottingham Health Profile	Non-significant
Arnold et al[2]	109	Short acting octreotide vs. short acting octreotide+ interferon-α	EORTC QLQ c30	Global health status* worse with combination
PROMID[3]	85	Octreotide LAR vs. Placebo	EORTC QLQ c30	Global health status* non-significant

*Only global health status results were reported

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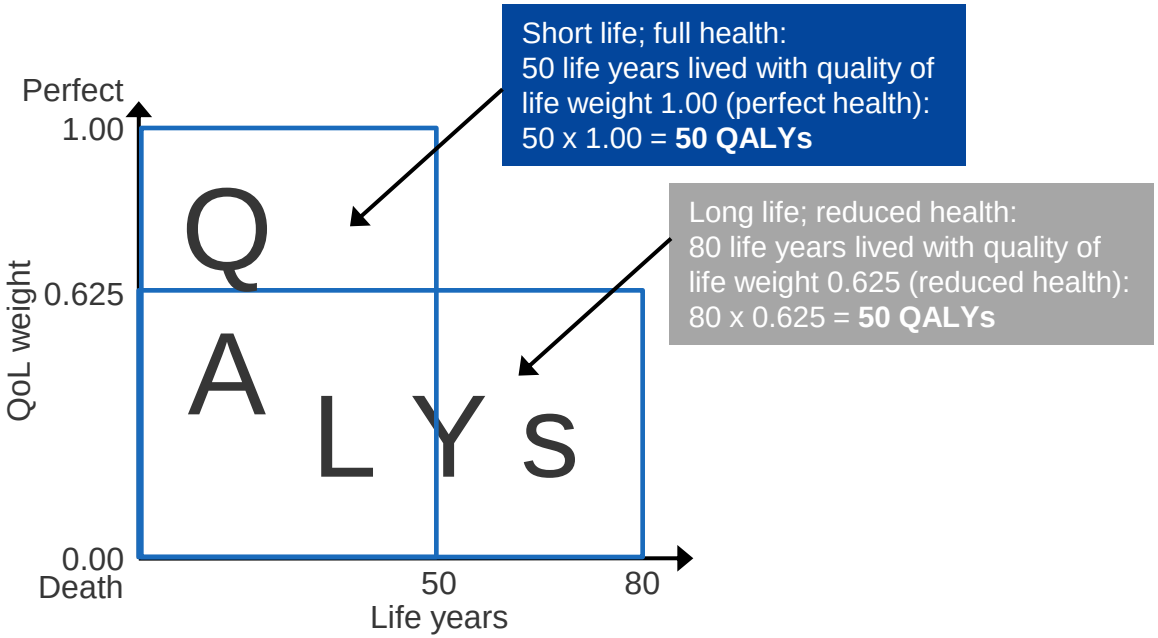
[1]O'toole et al Cancer 2000; [2]Arnold et al Clin Gastroenterol Hepatol 2005; [3]Rinke et al J Clin Oncol 2009

Cost-effectiveness analysis: Quality-adjusted life-year (QALY)



Treatment → initial improvement in QoL

Then adverse events might lead to worse QoL than no treatment

Then treated patient had a longer life despite lower QoL

$$\text{Cost Utility Ratio} = \frac{\text{Cost of Intervention A } \textit{minus} \text{ Cost of Intervention B}}{\text{No. of QALYs by Intervention A } \textit{minus} \text{ No. of QALYs by Intervention B}}$$

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Phillips C. What is a QALY? Second Edition 2009

Rare tumours of the GI tract

Cancers	Incidence
GEP NET	23 per million
GIST	6.5-14.5 per million
Extranodal MALT	11 per million

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High cost drugs reimbursement in the UK

Tumour	Incidence (per million)	High Cost Drugs	Reimbursement
GEP NET	23	Everolimus	√ NCDF
		Sunitinib	√ NCDF
GIST	6.5-14.5	Imatinib	√ NICE
		Sunitinib	√ NICE
		Regorafenib	√ NCDF
MALT	11	Rituximab	NHS

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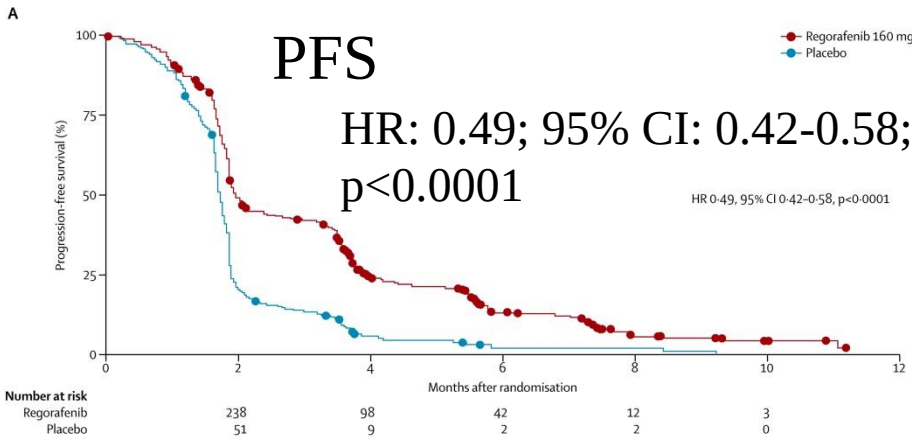
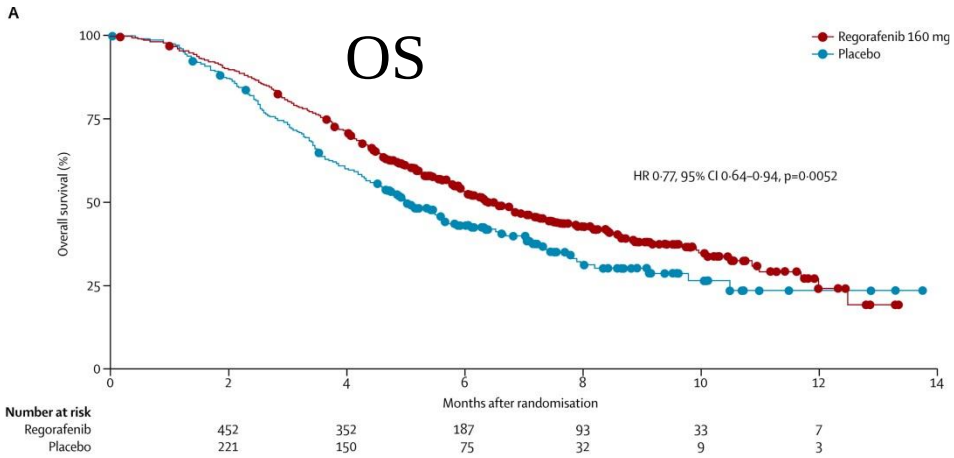
NCDF: National Cancer Drug Fund
NICE: National Institute for Health and Care Excellence
NHS: National Health Service

Regorafenib for CRC and GIST

Colorectal Cancer[1]

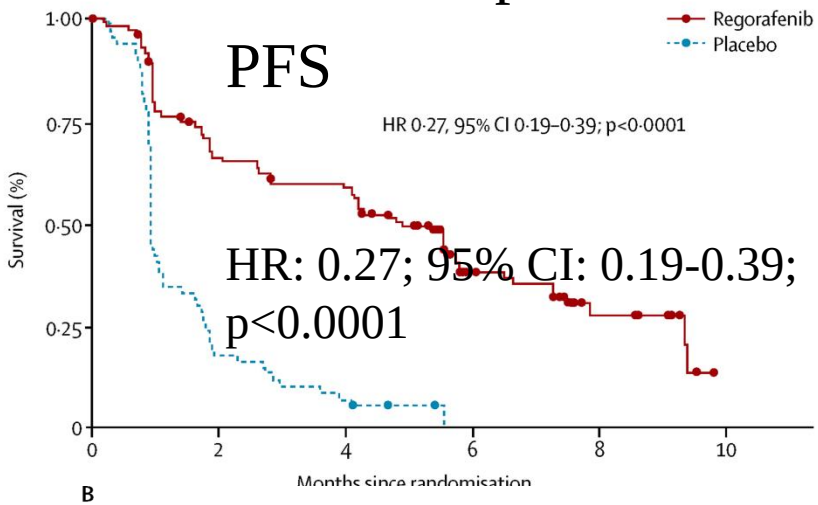
Incidence: 470 per million

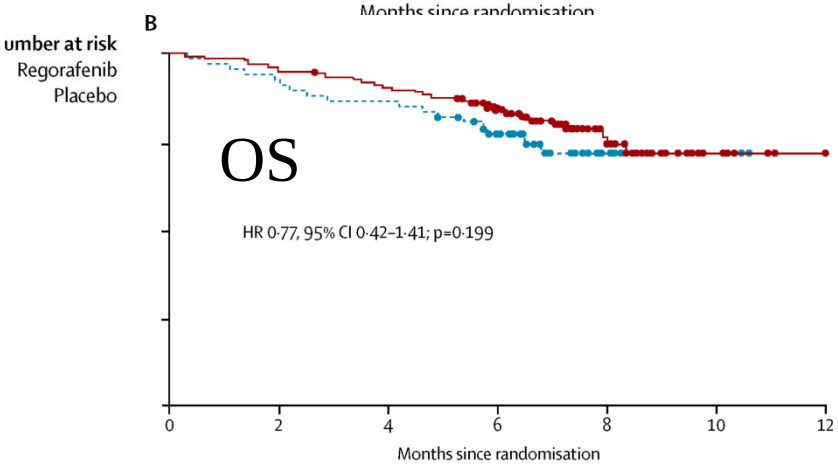




GIST[2]

Incidence: ~10 per million





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[1]Grothey et al Lancet 2013; [2]Demetri et al Lancet 2013

Conclusions

- Clinical trials on rare tumours with long overall survival pose challenge on defining an optimal primary endpoint
- Progression free survival is preferred but have significant limitations
- Quality of life measurement using the current available instruments does not correlate with survival outcome
- Society may be more willing to pay for more expensive treatment for rare cancers rather than common cancers given similar efficacy outcome, as there are less financial burden

Acknowledgement

National Health Service funding to the
National Institute for Health Research
Biomedical Research Centre

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NHS
National Institute for Health Research