Classical and targeted therapies in gastroentero-pancreatic neuroendocrine tumours

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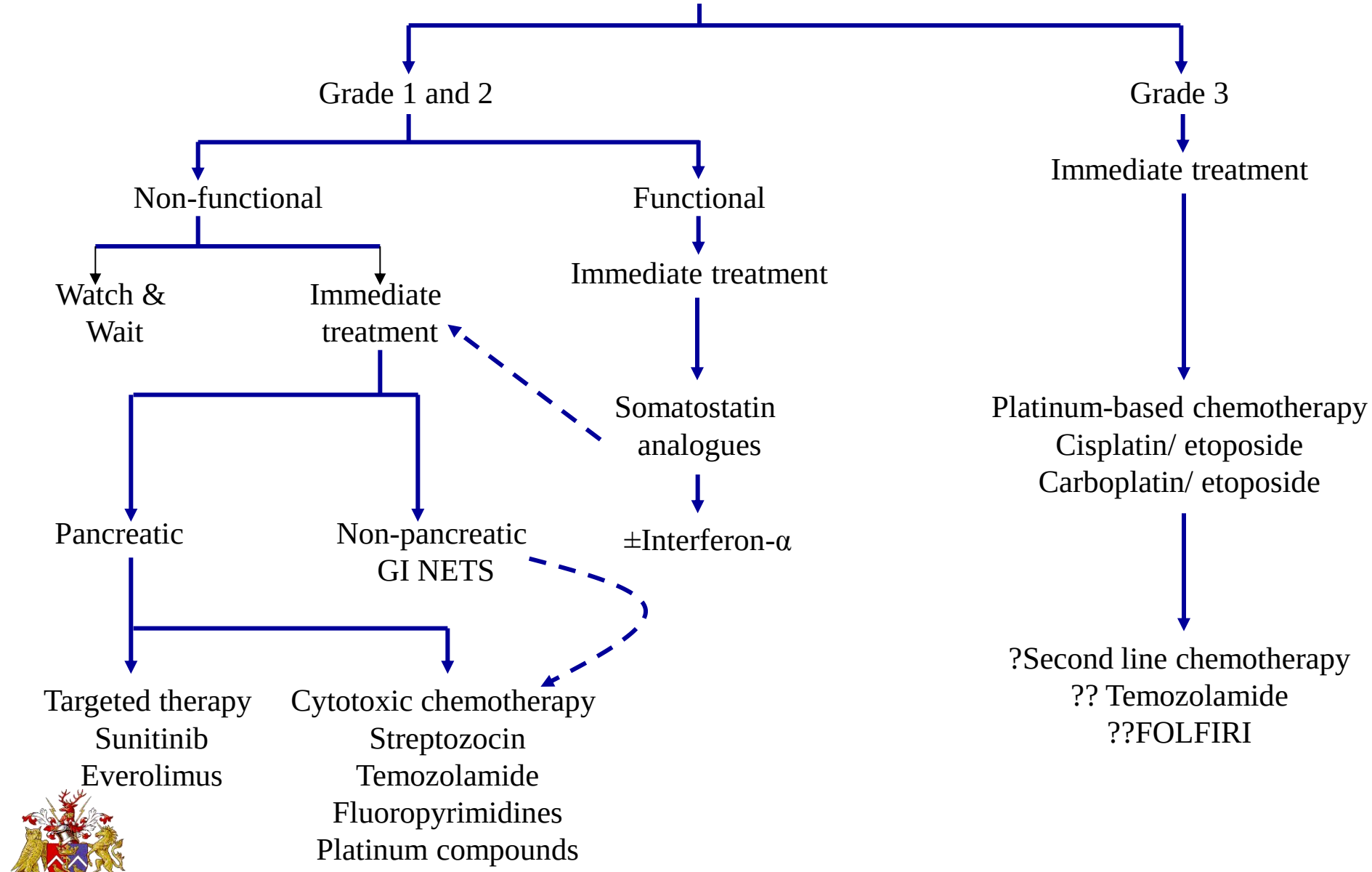
Disclosure

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

Systemic therapy for GEP NETs



THE ROYAL MARSDEN

Systemic therapy for GEP NETs

Grading of neuroendocrine tumour/carcinoma

Tumour differentiation	Mitotic count	Ki67
Grade 1 neuroendocrine tumour	<2/HPF	≤2%
Grade 2 neuroendocrine tumour	2-20/HPF	3-20%
Grade 3 neuroendocrine carcinoma	>20/HPF	>20%

Systemic therapy for GEP NETs

Grade 3

Immediate treatment

Platinum-based chemotherapy
Cisplatin/ etoposide
Carboplatin/ etoposide

?Second line chemotherapy
??Temozolamide
??FOLFIRI

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Grading of neuroendocrine tumour/carcinoma

Tumour differentiation	Mitotic count	Ki67
Grade 1 neuroendocrine tumour	<2/HPF	≤2%
Grade 2 neuroendocrine tumour	2-20/HPF	3-20%
Grade 3 neuroendocrine carcinoma - large cell - small cell	>20/HPF	>20%

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Survival for grade 3 GI NEC SEER database n=2546

Disease extent	Median Survival (months)	95% CI (months)
Localised	38	31-45
Regional	16	15-17
Distant	5	4.7-5.4

57% had distant disease

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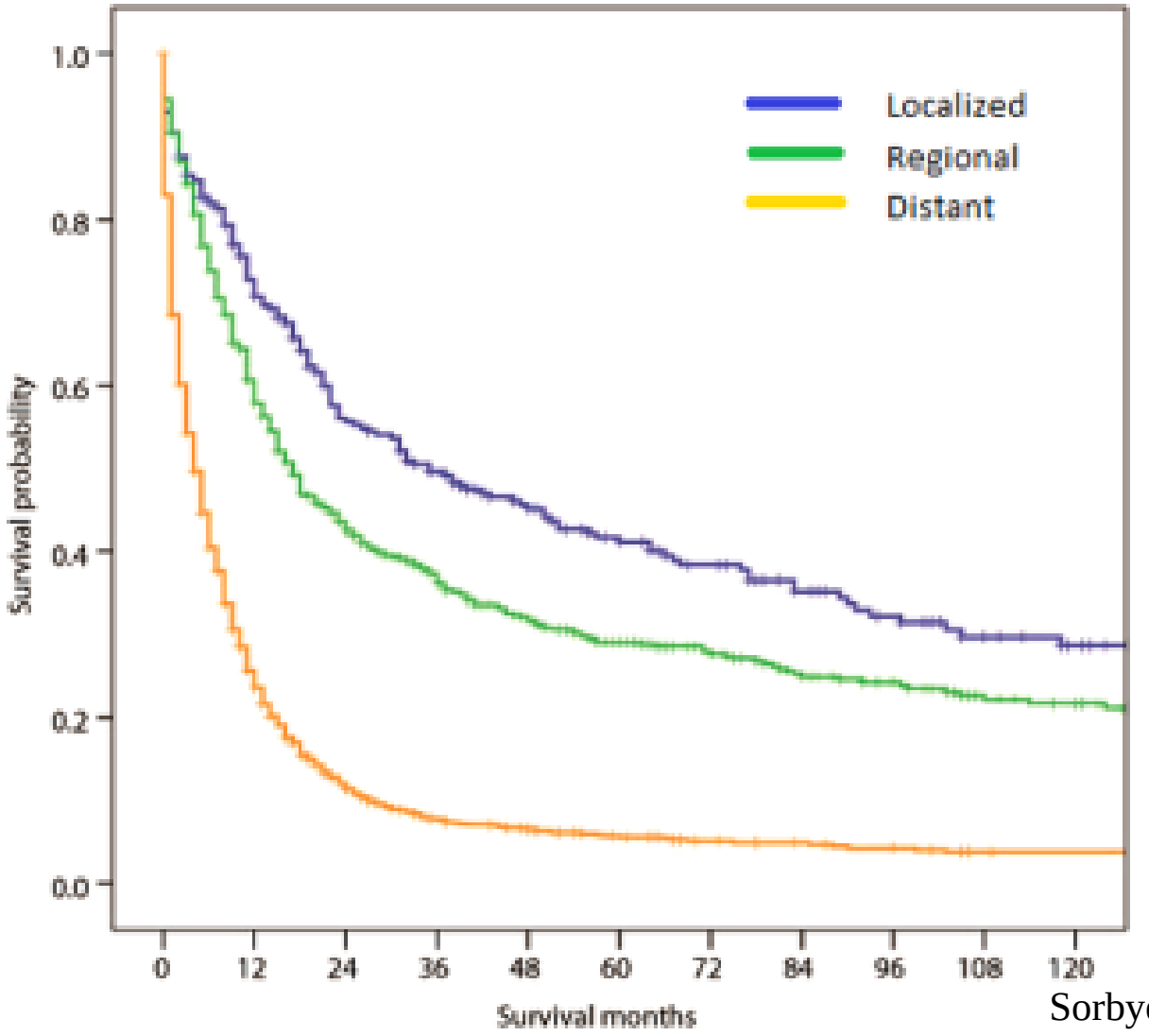
Sorbye et al Cancer 2014

Survival for grade 3 GI NEC SEER database n=2546



Sorbye et al Cancer 2014

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NORDIC NEC study

- Between 2000-2009
- N=305
  - 301 had metastatic disease
  - 3% had hormone related symptoms
- Palliative chemotherapy n=252
  - First line chemotherapy
    - Cisplatin/etoposide n=129
    - Carboplatin/etoposide n=67
    - Carboplatin/etoposdie/vincristine n=28
    - Other drugs n=28
  - Second line chemotherapy n=100
    - Temozolamide n=35
    - Docetaxel n=20
  - Third line chemotherapy n=31

Sorbye et al Ann Oncol 2013

Treatment efficacy

	n	ORR	SD	PD	PFS	OS
First line chemotherapy						
All patients	252	31%	33%	36%	4 months	11 months
Ki67 <55%	136	15%	47%	38%	4 months	14 months
Ki67 ≥55%	154	42%	24%	34%	4 months	10 months
Morphology						
Small cell	117	36%	33%	31%	5 months	12 months
Non small cell	154	28%	34%	38%	4 months	11 months
Second line chemotherapy						
	84	18%	33%	49%	NR	NR

No Rx
1 month

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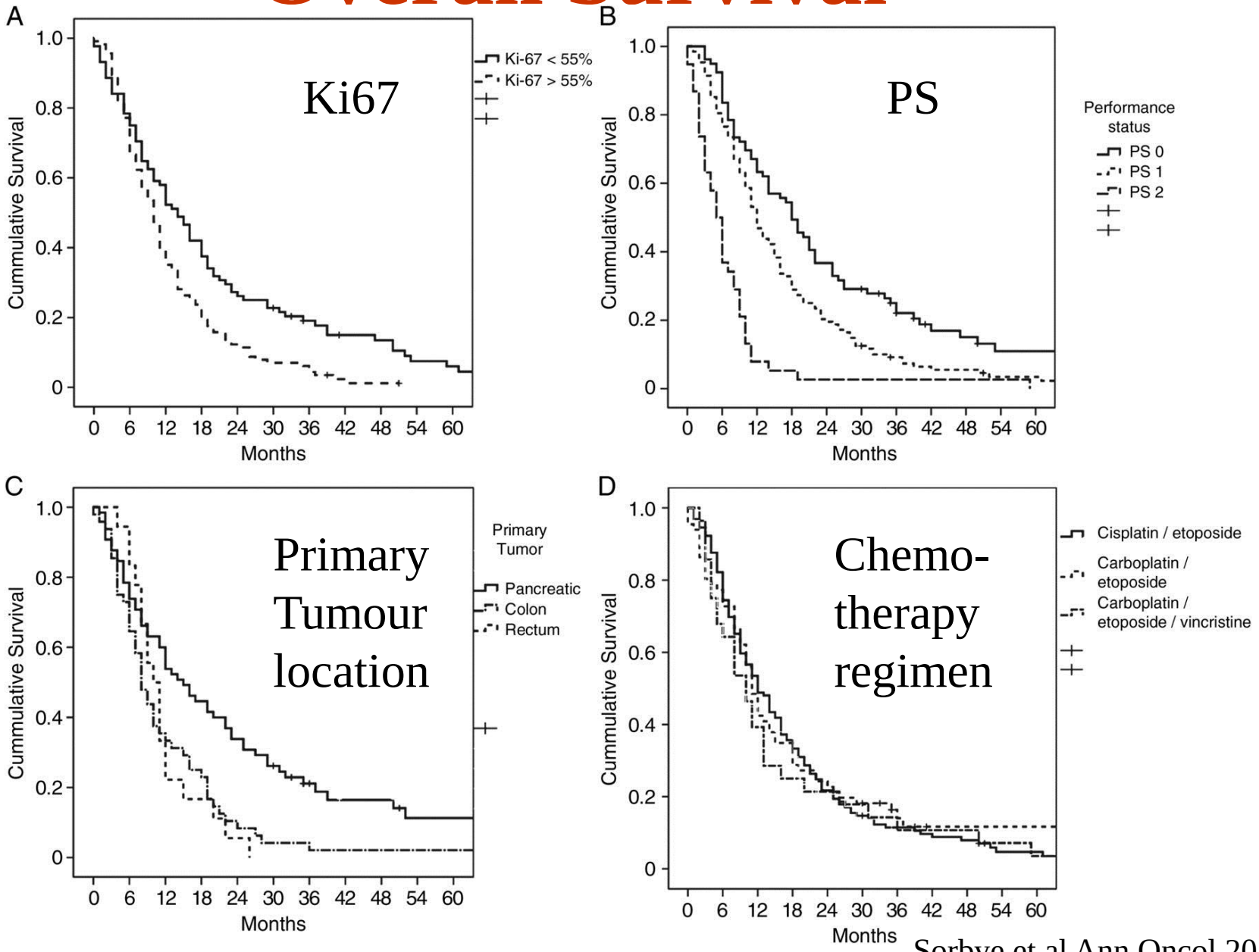
Sorbye et al Ann Oncol 2013

Overall Survival



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Sorbye et al Ann Oncol 2013

Second line chemotherapy for grade 3 NEC

	Rx	n	ORR	SD	PD	PFS (months)	OS (months)
France[1]	FOLFIRI	19	31%	31%	38%	4	18
	No treatment	20					6.8
Sweden +Norway[2]	Temozolamide ± capecitabine	25	33%	38%	29%	6	22
NORDIC[3]	Various*	84	18%	33%	49%	NR	NR

*temozolomide-based chemotherapy n=35
docetaxel-based chemotherapy n=20

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[1]Hentic et al Endocr Relat Cancer 2012; 2Welin et al Cancer 2011; [3]Sorbye et al Ann Oncol 2013

Systemic therapy for GEP NETs

Grade 3

Immediate treatment

Platinum-based chemotherapy
Cisplatin/ etoposide
Carboplatin/ etoposide

?Second line chemotherapy
??Temozolamide
??FOLFIRI

No randomised controlled trials
for first line or subsequent line therapy

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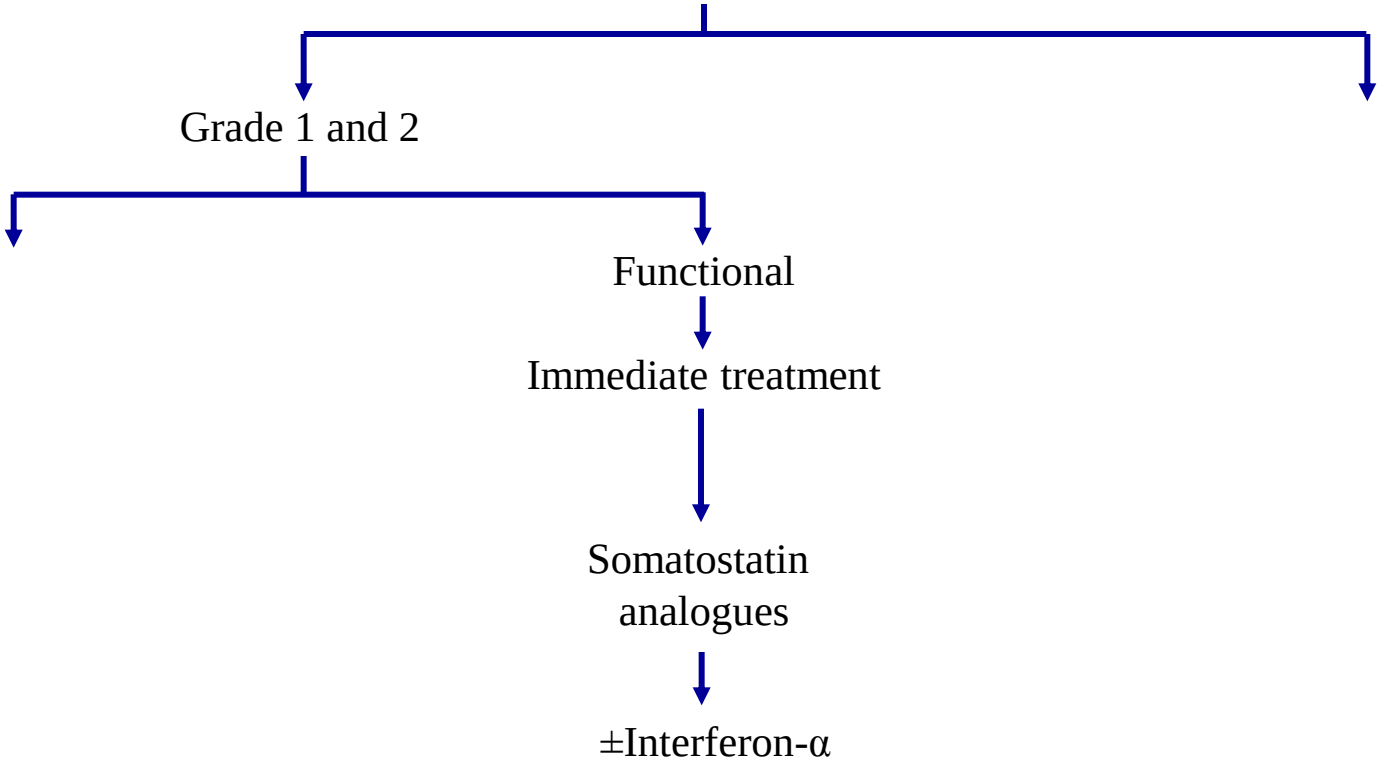
Systemic therapy for GEP NETs



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Somatostatin receptors and octreotide

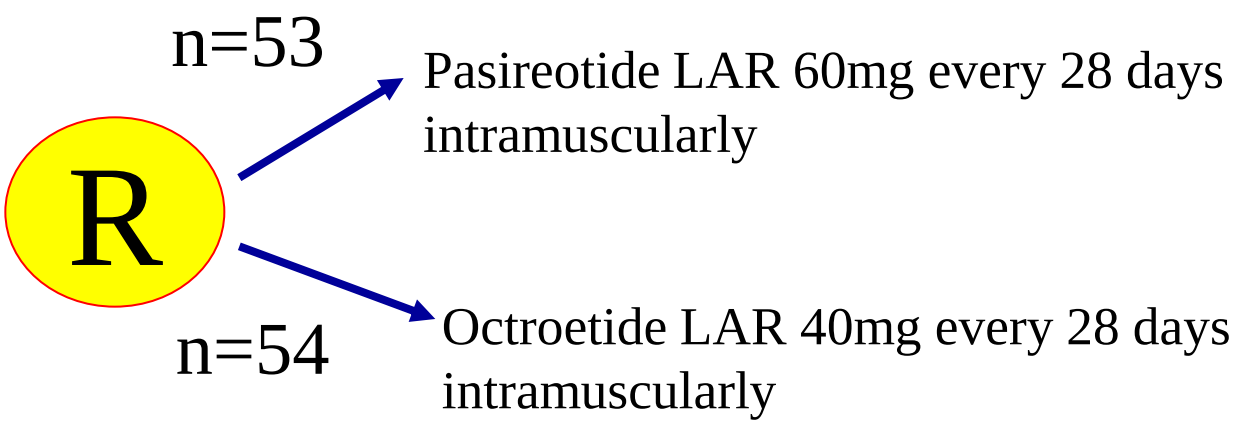
	sst_1	sst_2	sst_3	sst_4	sst_5
Carcinoid tumours SSR expression	76%	80%	43%	68%	77%
Binding affinity IC_{50} (nmol/l)					
Octreotide	280.0	0.38	7.10	>1000	6.30
Pasireotide	9.3	1.0	1.5	>1000	0.16

THE ROYAL MARSDEN

Schmid HA Mol Cell Endocrinol 2008

Randomised phase III study of pasireotide LAR versus octreotide LAR

Functional NET patients with inadequate control of symptoms (diarrhoea ± flushing) while receiving treatment with maximum approved dose of currently available of SSRA for ≥3 months



Primary endpoint: Symptom response at month 6
Secondary endpoints: Tumour response
Safety
Exploratory endpoint: Progression free survival

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Wolin et al ASCO 2013

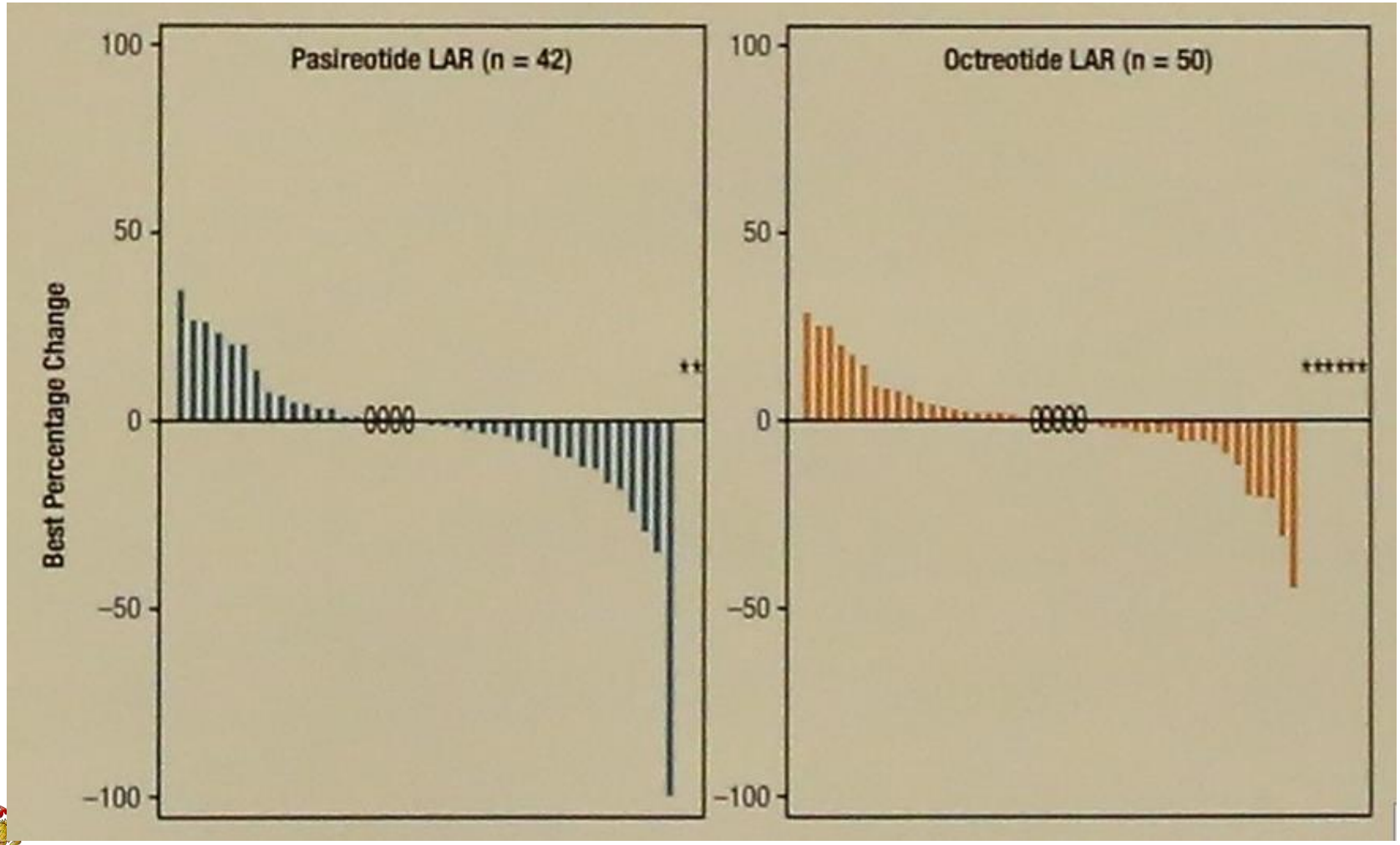
Randomised phase III study of pasireotide LAR versus octreotide LAR

	Pasireotide LAR	Octreotide LAR
Symptom response at month six		
Diarrhoea + flushing	5/37 (13.5%)	11/39 (28.2%)
Odds Ratio: 0.40 (95%: 0.12 - 1.29)		
Predominantly diarrhoea	2/2 (100%)	1/5 (20%)
Predominantly flushing	2/4 (50%)	0/1(0%)
Overall	9/43 (20.9%)	12/45 (26.7%)
Odds Ratio: 0.73 (95%: 0.27 - 1.99); p=0.53		
Radiological disease control	37/51 (73%)	39/42 (75%)
Odds Ratio: 0.88 (95%: 0.37 – 2.12); p=0.778		

THE ROYAL MARSDEN

Wolin et al ASCO 2013

Randomised phase III study of pasireotide LAR versus octreotide LAR



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Wolin et al ASCO 2013

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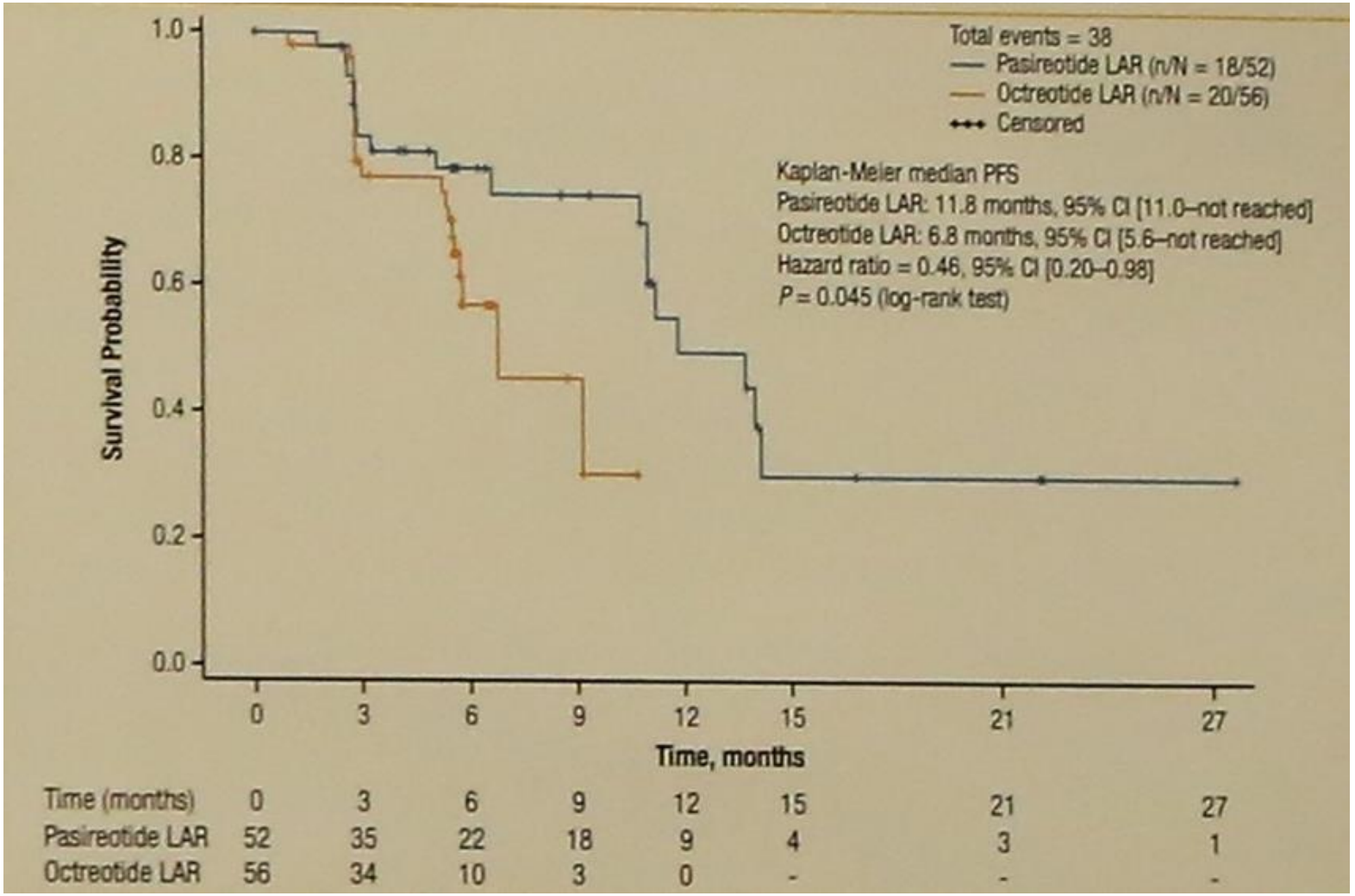

THE ROYAL MARSDEN

Wolin et al ASCO 2013

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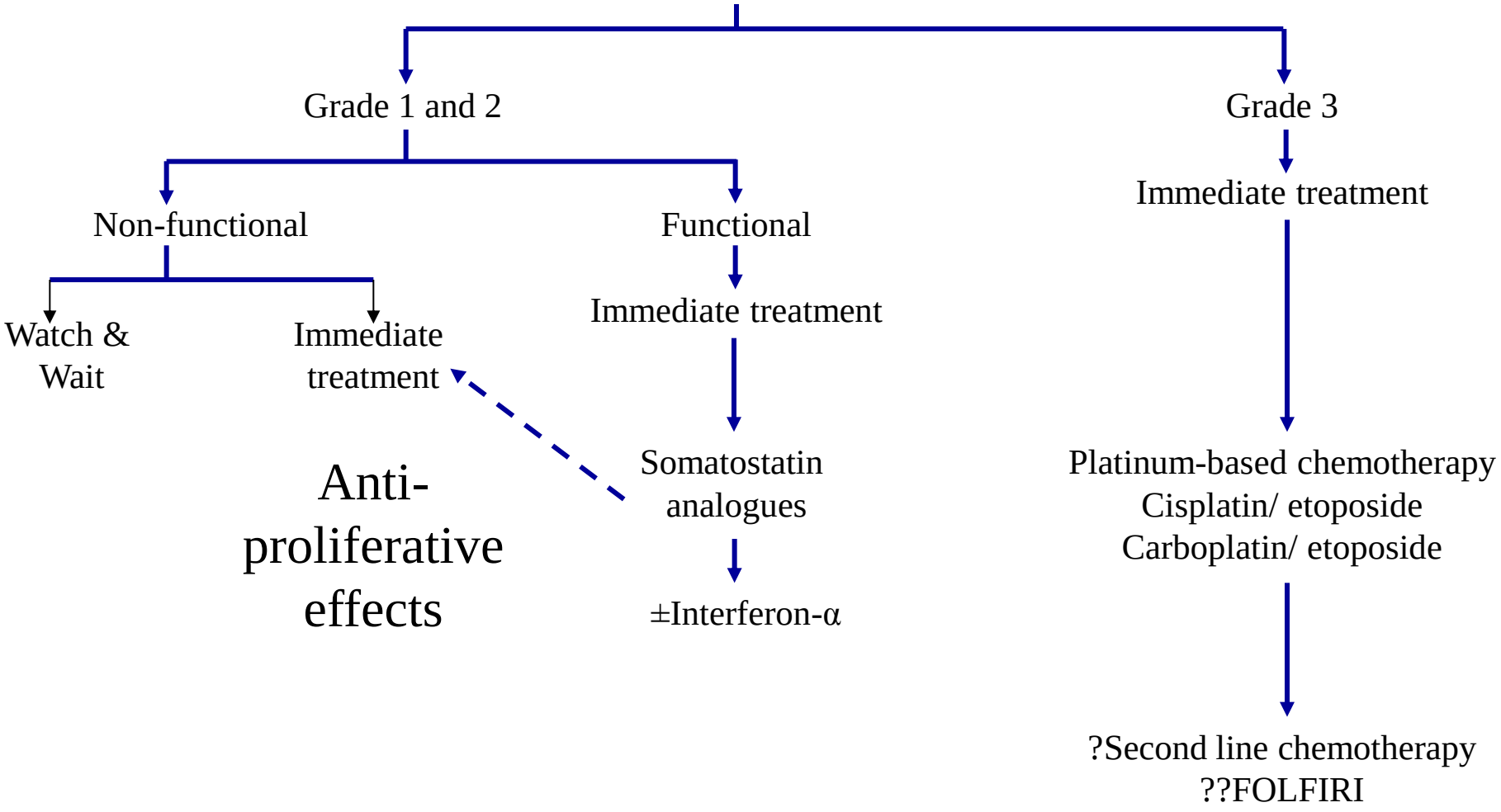

Placebo-controlled RCTs of somatostatin analogues as anti-proliferative agents

	PROMID[1]		CLARINET[2]	
	OCT	PBO	LAR	PBO
N	42	43	101	103
Dose	30mg	NA	120mg	NA
No PD before study entry	Not reported		96% of patients	
Proliferation index				
Ki67 0-2%	97.6%	93%	68%	70%
Ki67 3-10%	NR	NR	32%	28%
Primary tumour location				
Pancreas	0%	0%	42%	48%
Midgut	100%	100%	33%	39%
Hindgut	0%	0%	11%	3%

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[1]Rinke et al J Clin Oncol 2009; [2]Caplin et al N Engl J Med 2014

Placebo-controlled RCTs of somatostatin analogues as anti-proliferative agents

	PROMID[1]		CLARINET[2]	
	OCT	PBO	LAR	PBO
N	42	43	101	103
Primary tumour resected	69%	63%	40%	38%
Hepatic tumour volume >25%	16.7%	20.9%	39%	28%
Elevated chromogranin A	61.9%	69.8%	66%	64%

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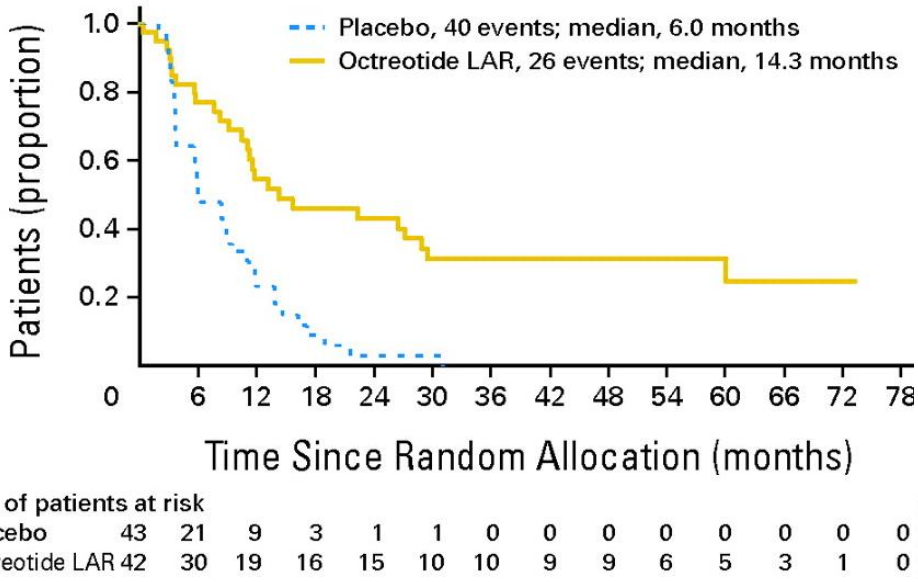
[1]Rinke et al J Clin Oncol 2009; [2]Caplin et al N Engl J Med 2014

PROMID and CLARINET primary outcome

PROMID[1]

TTP: Octreotide LAR vs placebo

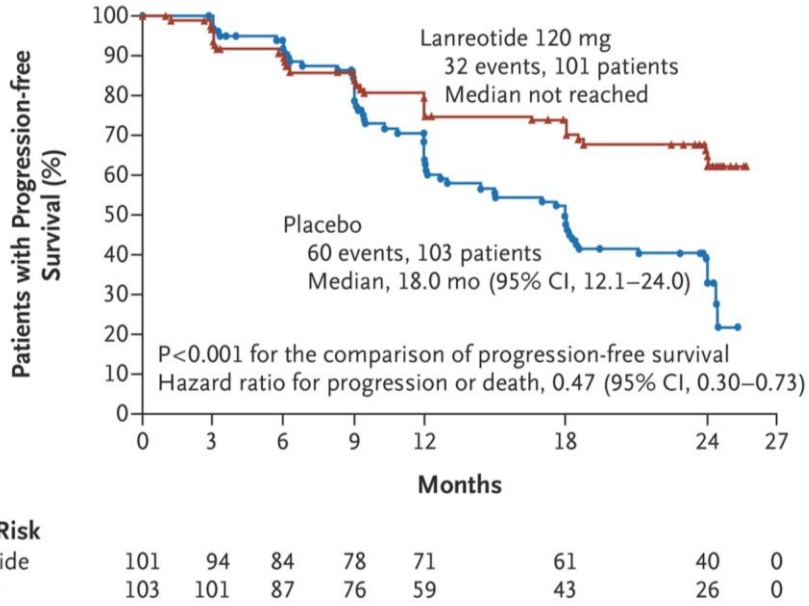


	OCT	PBO
Median TTP	14.3 months	6.0 months

HR: 0.34; 95% CI: 0.20-0.59; p=0.000072

CLARINET[2]

PFS: Lanreotide vs placebo



	LAN	PBO
Median PFS	Not reached	18 months

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

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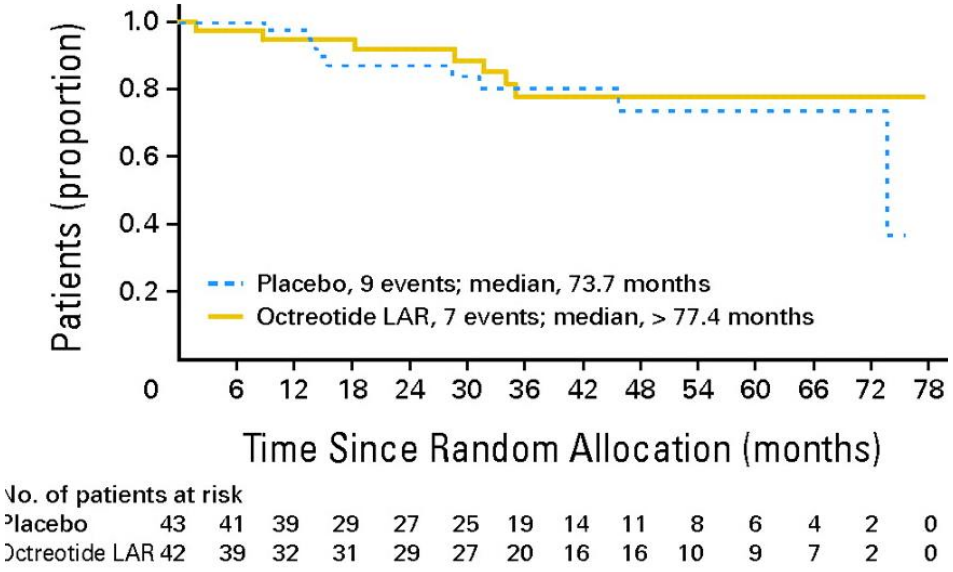
[1]Rinke et al J Clin Oncol 2009; [2]Caplin et al N Engl J Med 2014

Overall survival

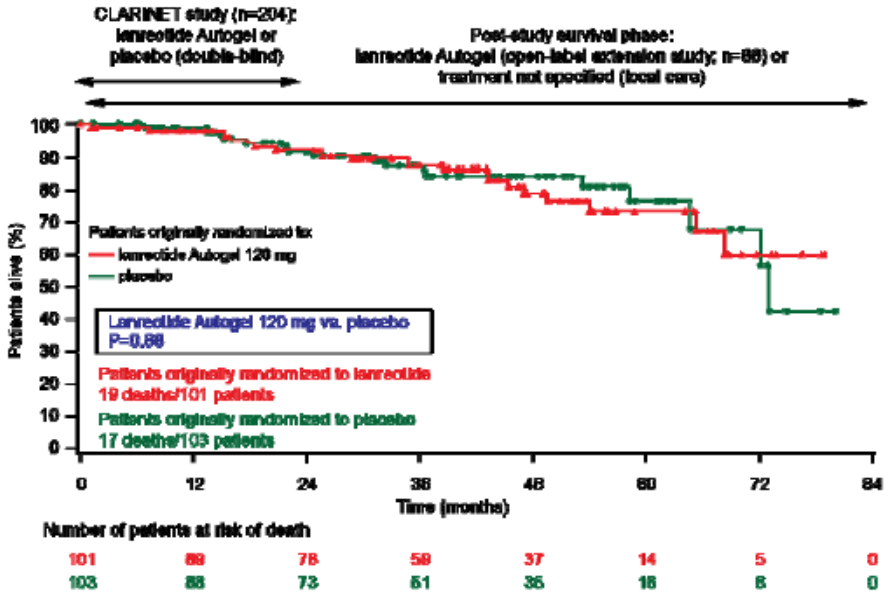
PROMID[1,2]
OS: Octreotide LAR vs placebo



	OCT	PBO
Median OS[2]	Not reached	84 months

HR:0.85; 95% CI: 0.46-1.56; p=0.59

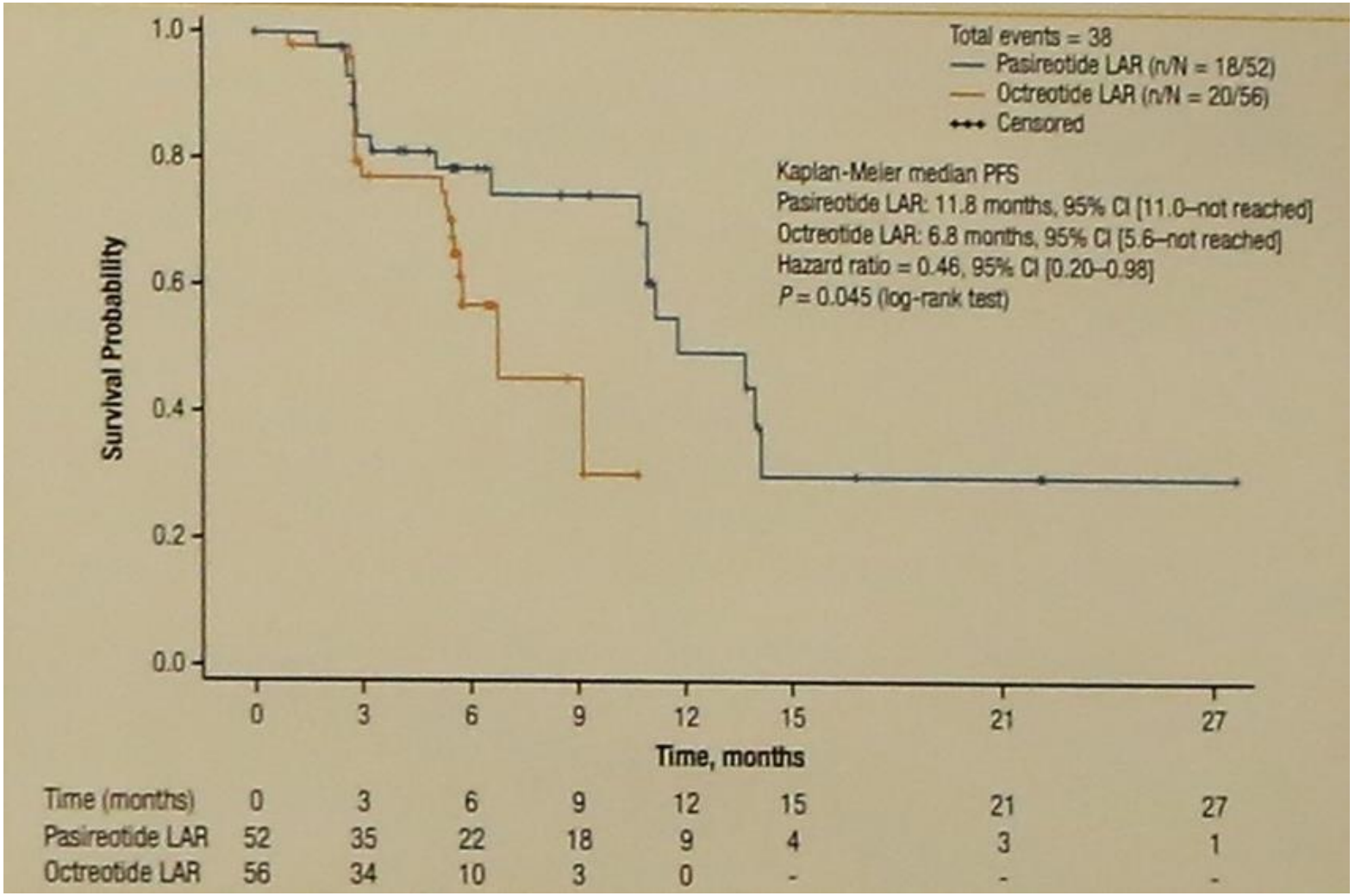
CLARINET[3]
OS: Lanreotide vs placebo



THE ROYAL MARSDEN

[1]Rinke et al J Clin Oncol 2009; [2]Arnold et al ASCO 2013; [3]Caplin et al N Engl J Med 2014

Randomised phase III study of pasireotide LAR versus octreotide LAR



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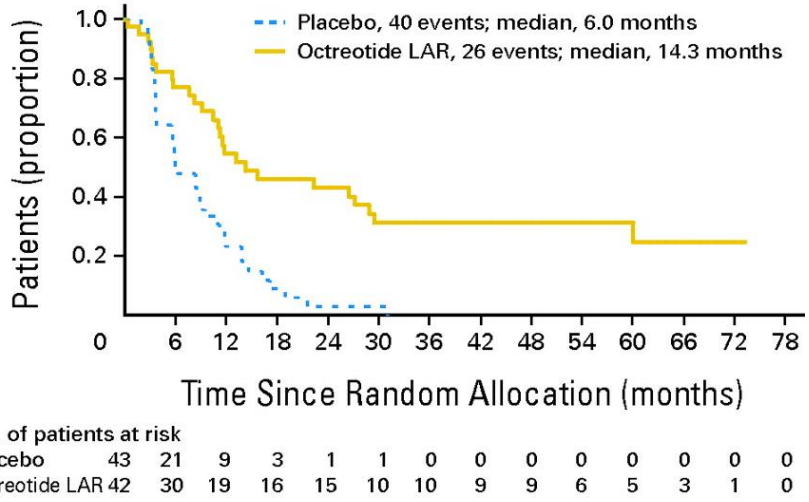
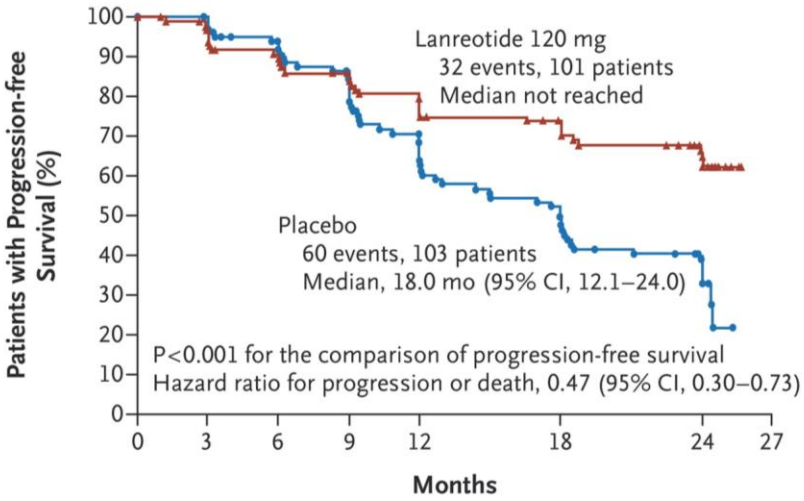
Wolin et al ASCO 2013

RCTs of neuroendocrine tumours
↑PFS ≠ ↑QoL

Study	n	Treatment arms	QoL instrument	Results
PROMID[1]	85	Octreotide LAR vs. Placebo	EORTC QLQ c30	Global health status non-significant
CLARINET[2]	204	Lanreotide vs. Placebo	EORTC QLQ c30	Global health status non-significant



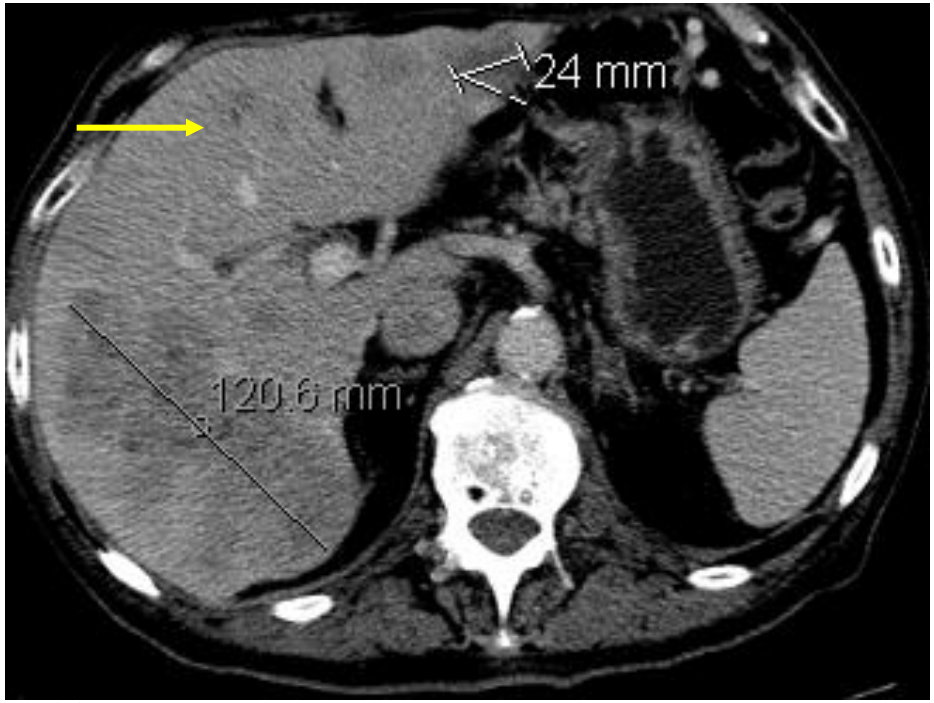


THE ROYAL MARSDEN

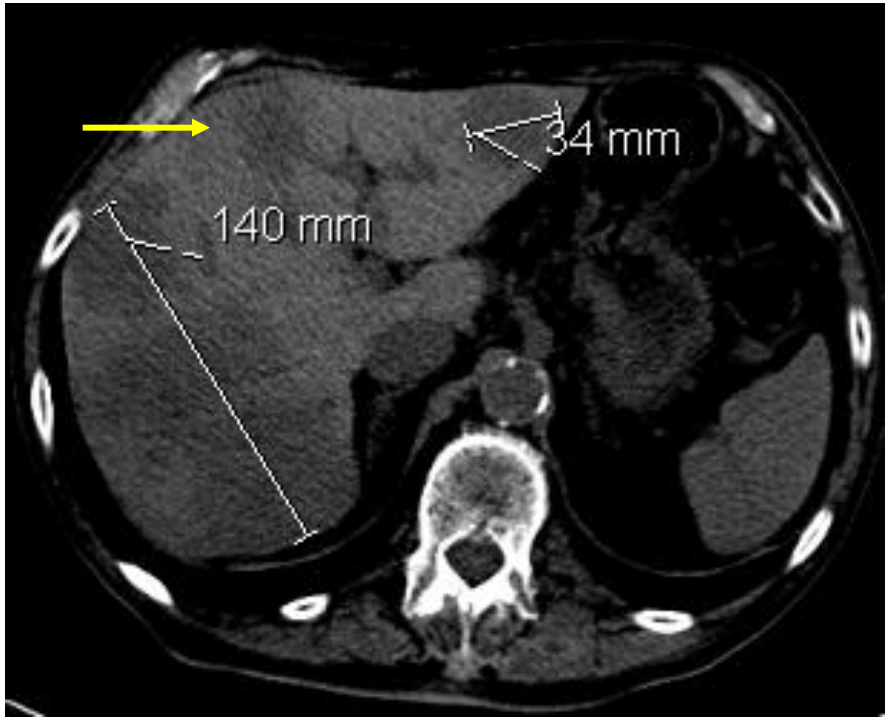
[1]Rinke et al J Clin Oncol 2009; [2]Caplan et al N Engl J Med 2014

Pancreatic NET with liver metastases: disease progression but asymptomatic

October 2012



September 2013



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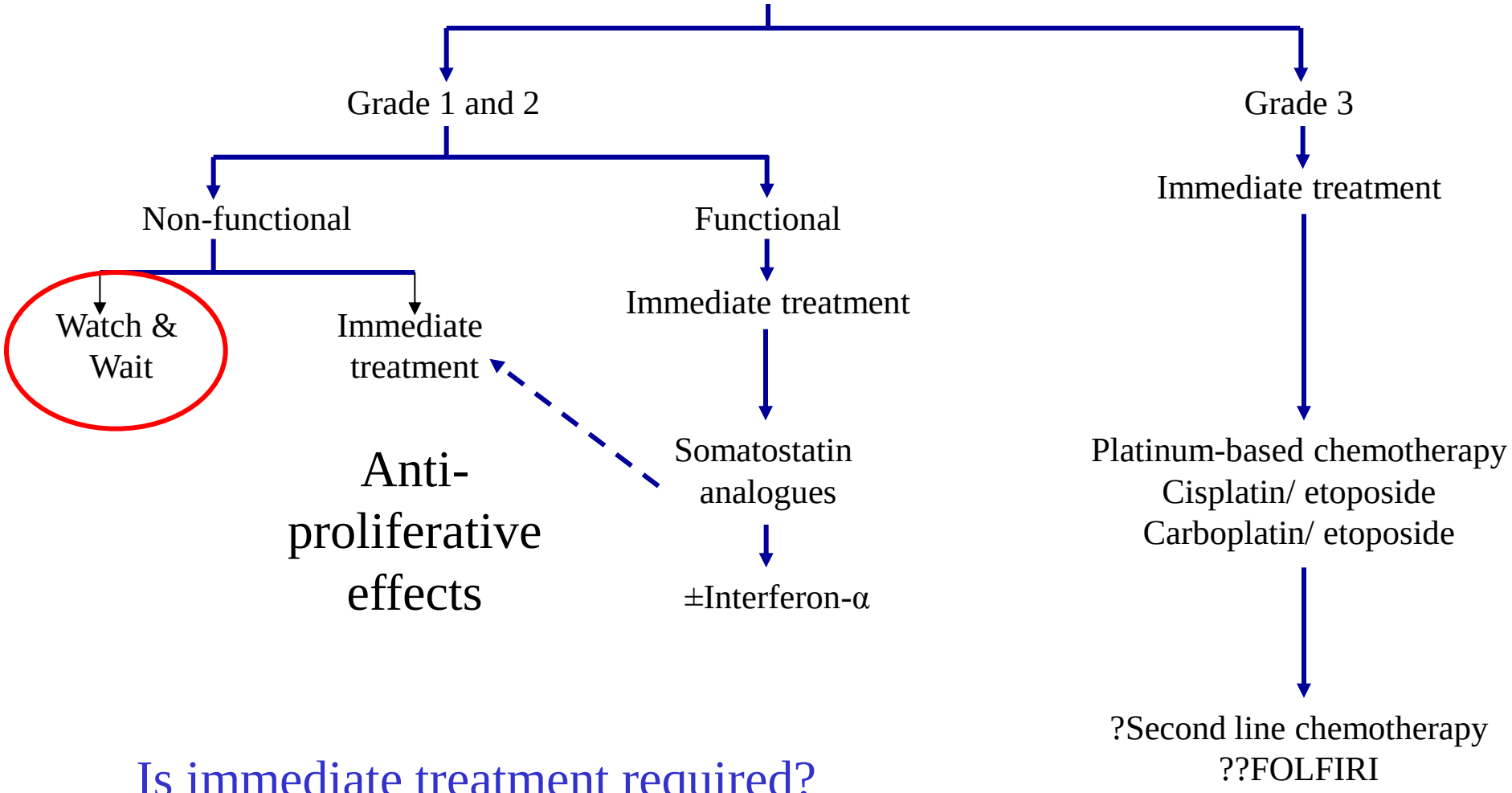
Systemic therapy for GEP NETs



Is immediate treatment required?

Patients may have asymptomatic disease progression and no improvement in QoL has been demonstrated yet

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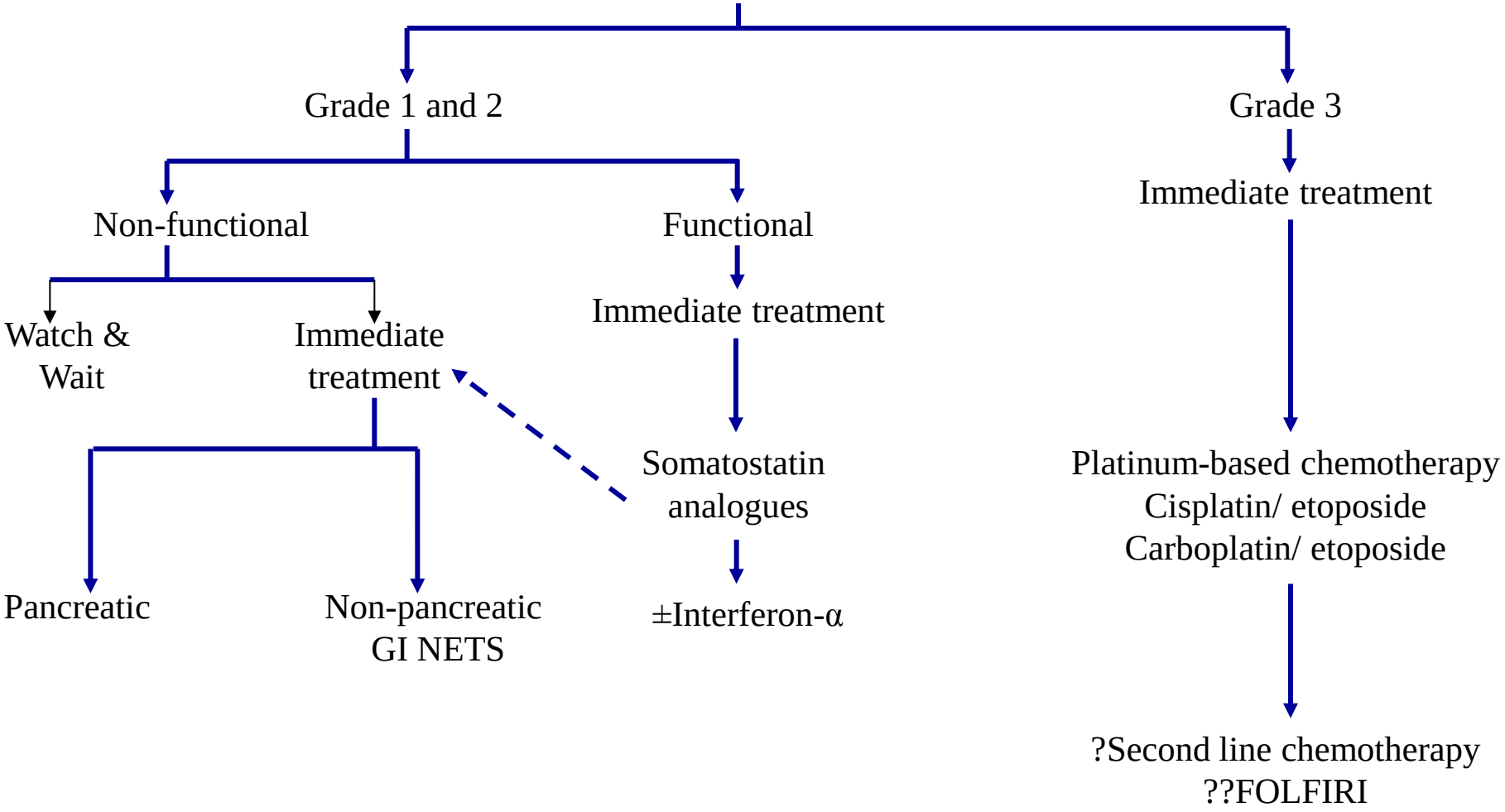
Systemic therapy for GEP NETs



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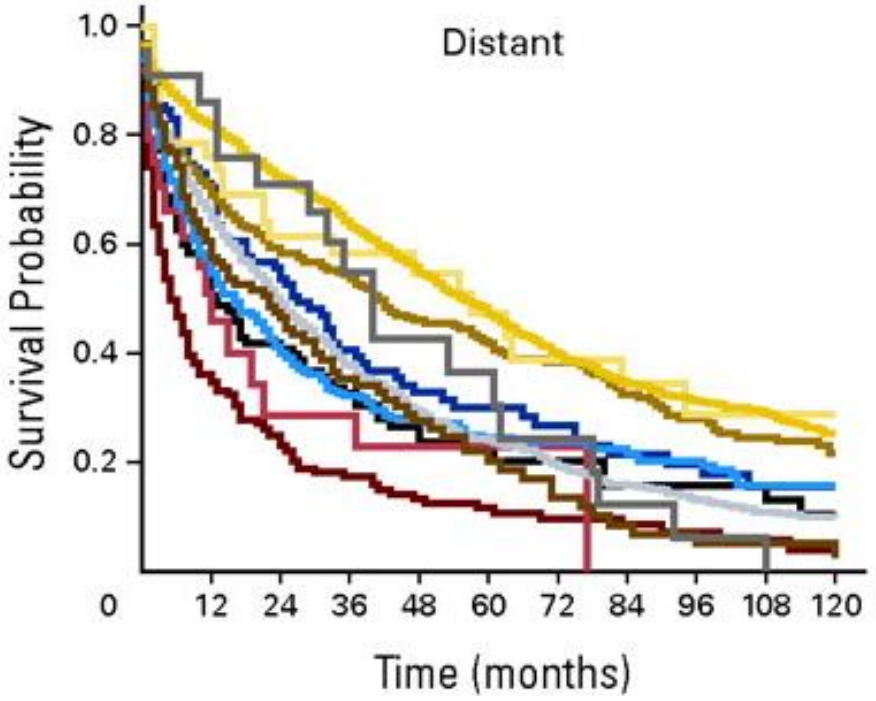
Overall survival by primary tumour location
SEER database n=35,618

Color	Site	Median Survival (months) Localized	Regional	Distant
	Appendix	>360	>360	27
	Cecum	135	107	41
	Colon	261	36	5
	Duodenum	107	101	57
	Gastric	154	71	13
	Liver	50	14	12
	Lung	227	154	16
	Pancreas	136	77	24
	Rectum	290	90	22
	Small bowel	111	105	56
	Thymus	110	68	40



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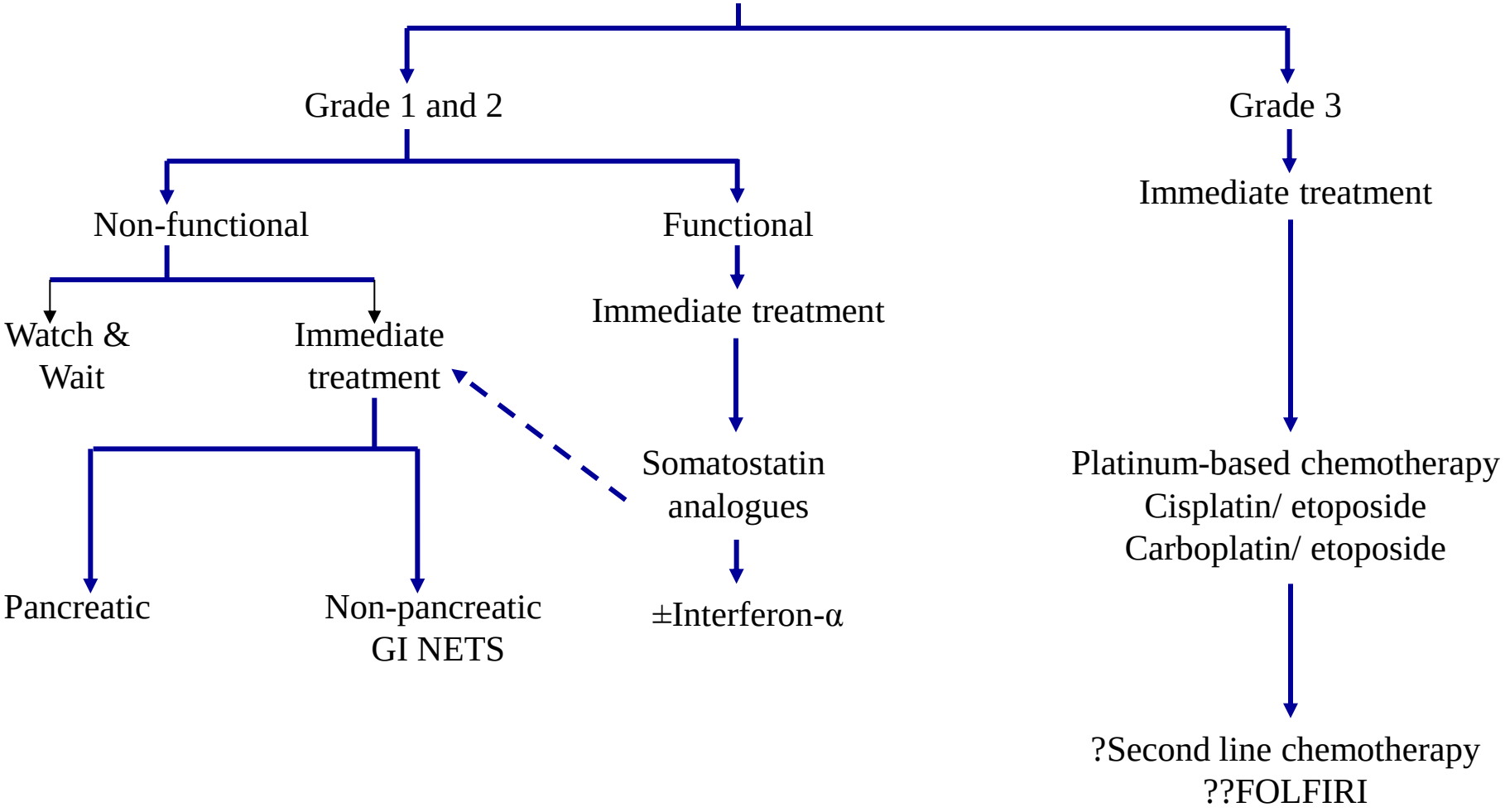
Systemic therapy for GEP NETs



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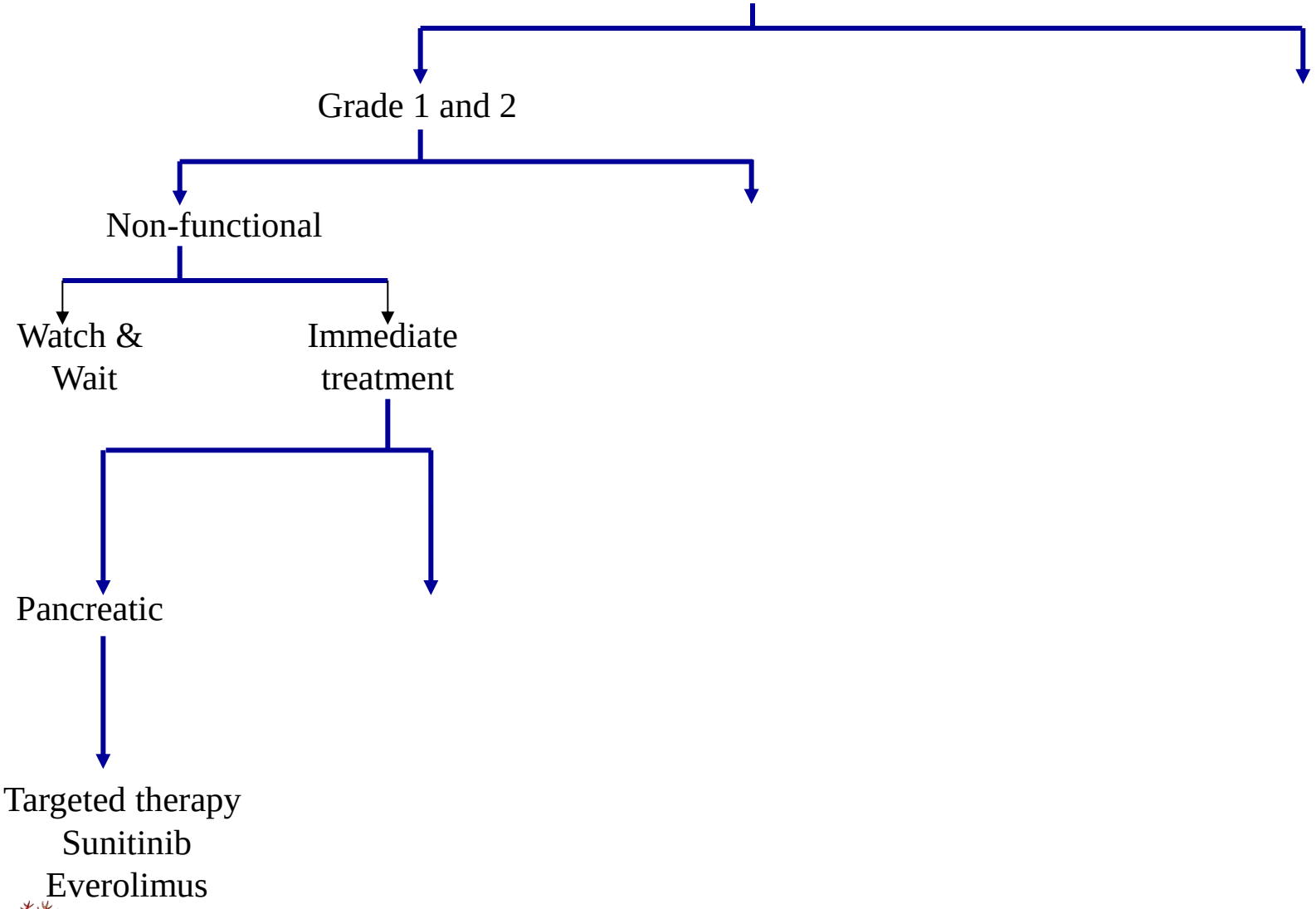
Systemic therapy for GEP NETs



THE ROYAL MARSDEN

Phase III placebo-controlled sunitinib study in pNET (A6181111 study)

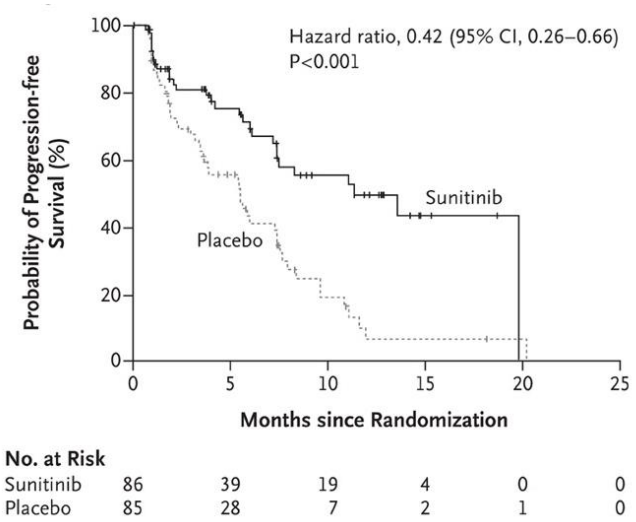
Well differentiated advanced pancreatic NET with radiological PD within 12 months
Either chemonaïve (31%) or chemo pretreated (69%)

n=86 → Sunitinib 37.5mg once daily

R

n=85 → Placebo

PFS: Sunitinib vs placebo[1]

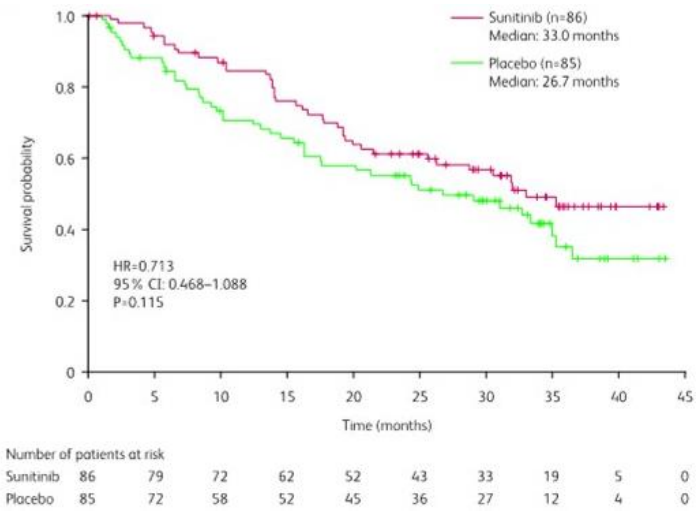


SU PBO

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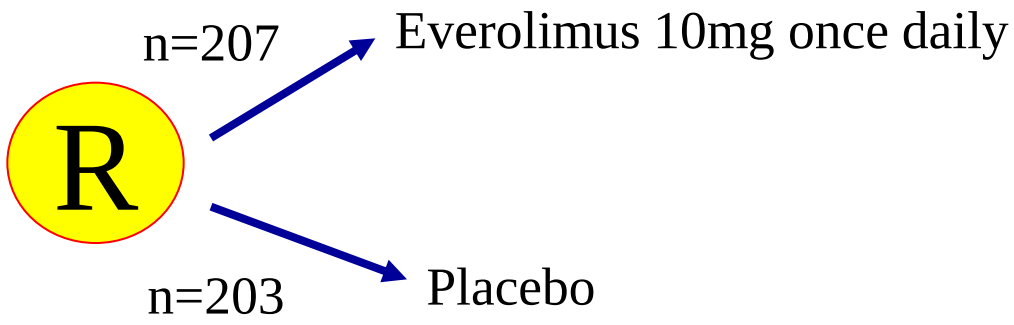
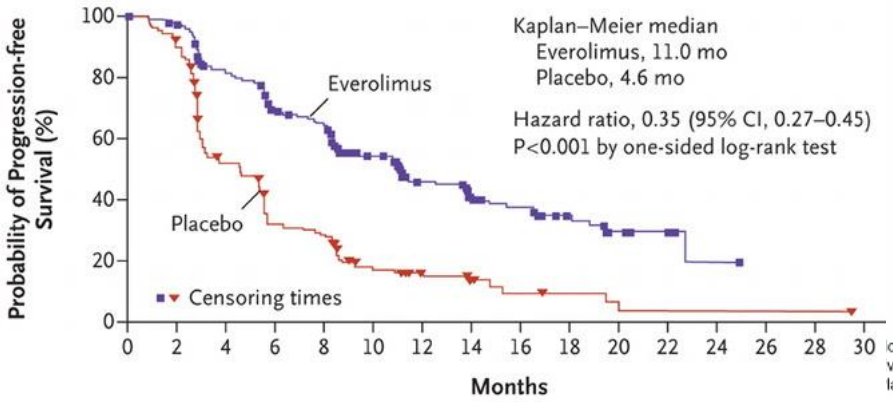
[1]Raymond et al N Engl J Med 2011; [2]Vinik et al ASCO 2012

Phase III placebo-controlled everolimus study in pNET (RADIANT 3 study)

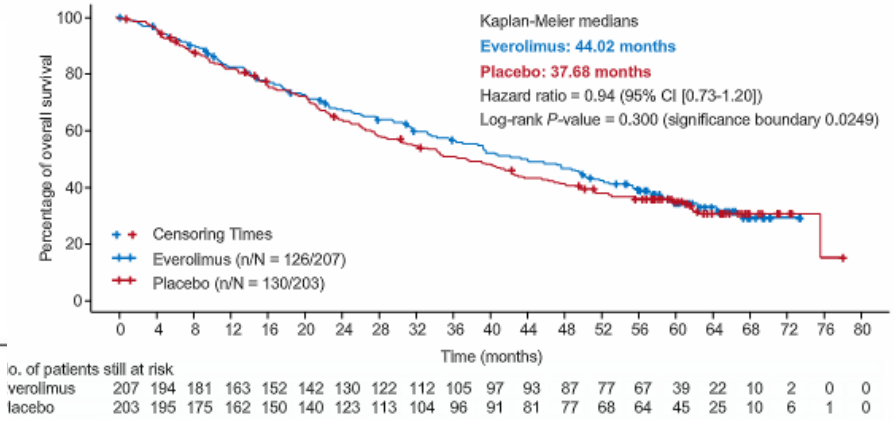
Well (83%) or moderately (16%) differentiated advanced pancreatic NET with radiological PD within 12 months
Either chemonaïve (54%) or chemo pretreated (46%)



PFS: Everolimus vs placebo[1]



OS: Everolimus vs placebo[2]



	EVE	PBO
Median PFS	11.0 months	4.6 months

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

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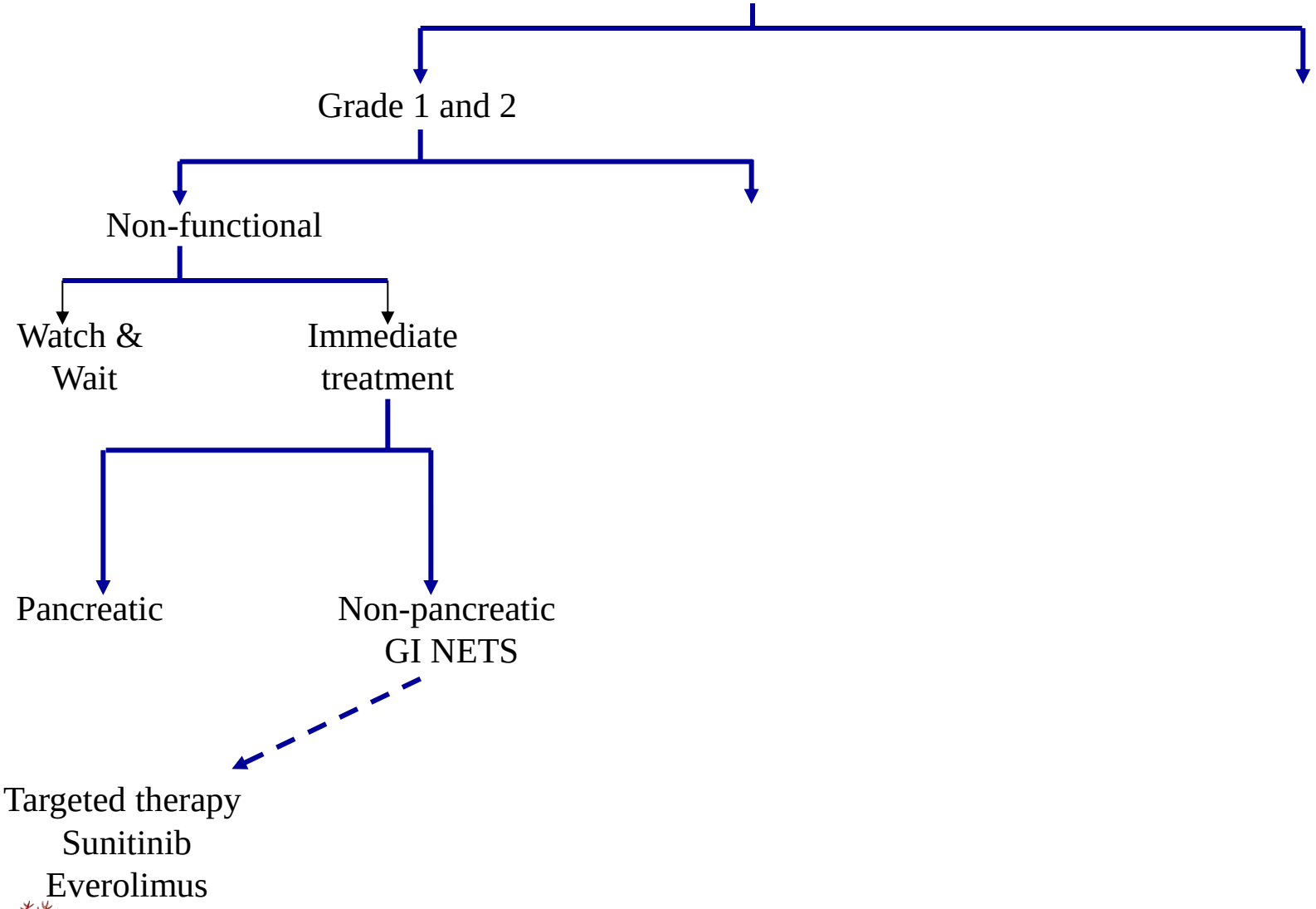
[1]Yao et al N Engl J Med 2011; [2]Yao et al ESMO 2014

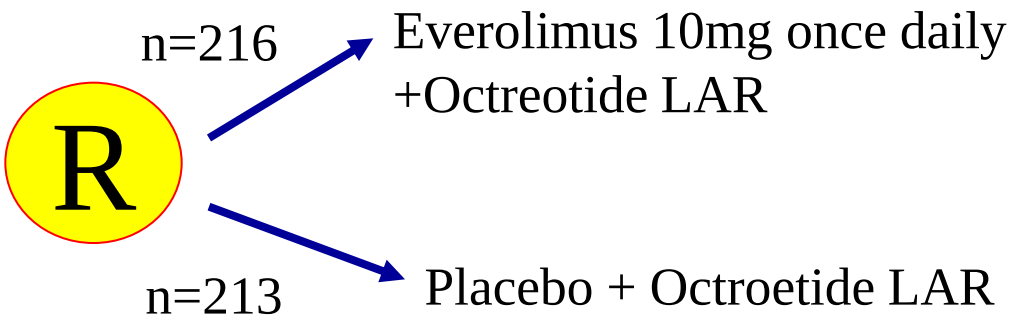
Systemic therapy for GEP NETs



THE ROYAL MARSDEN

Phase III placebo-controlled everolimus + octreotide study in functional NET (RADIANT 2 study)

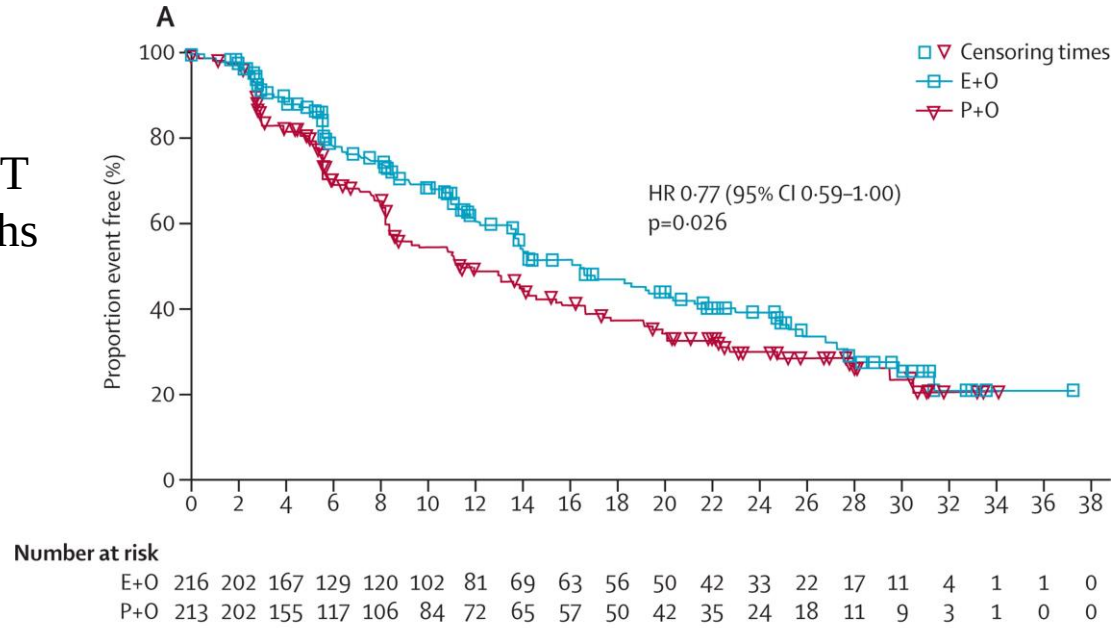
Well (79%) or moderately (16%) differentiated advanced functioning NET with radiological PD within 12 months
Primary small bowel (53%) or colon (7%)



Adjusted for two interim analyses and the final number of progression-free survival events recorded, the significance boundary on the p-value scale at final analysis was 0·0246.

	EVE +OCT	PBO+OCT
Median PFS	16.4 months	11.3 months

HR: 0.77; 95% CI: 0.59-1.00; p=0.026



Pavel et al Lancet 2011

THE ROYAL MARSDEN

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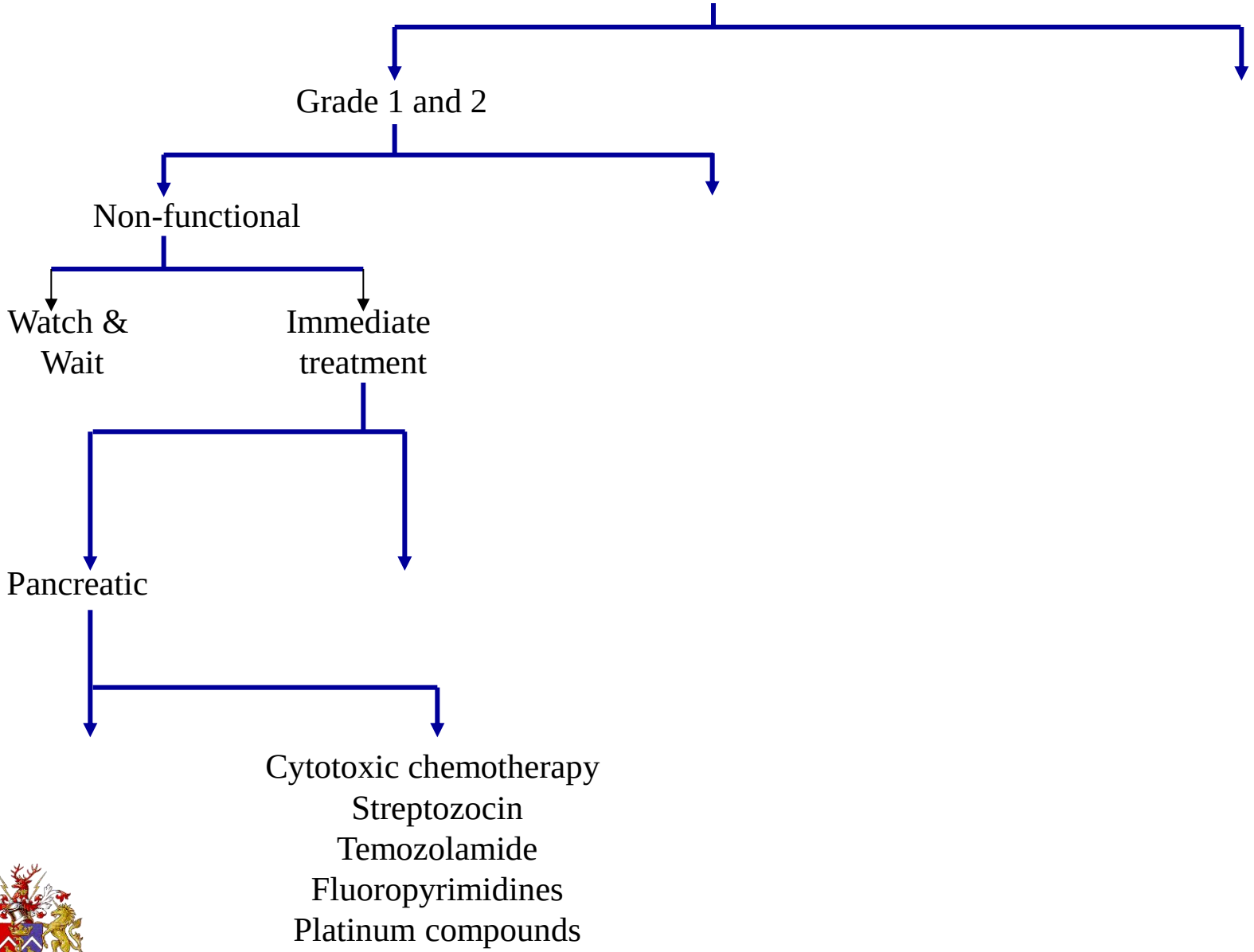

THE ROYAL MARSDEN

Cytotoxic chemotherapy for pancreatic NET

Regimen	Patients	Objective response (%)	PFS (m)	OS (m)	First author
Chlorozotocin	33	30	17*	18.0	Moertel (1992)
Chloroz + FU	44	36	11	25	Bukowski (1992)
FU + Strepto	33	45	14*	16.8	Moertel (1992)
Dox + Strepto	36	69	18*	26.4	Moertel (1992)
Dox + Strepto	16	6	3.9	20.2	McCollum (2004)
Dox + Strepto	16	6	18	Nr	Cheng (1999)
DTIC	50	34	Nr	19.3	Ramanathan (2001)
FU + Strepto + CDDP	49	38	Nr	Nr	Turner (2010)
Temoz + Thalido	11	45	Nr	Nr	Kulke (2006)
Temoz + Bev	17	24	8.6	Nr	Kulke (2006)
Strepto + Dox + FU	84	39	18	37	Kouvaraki (2004)
FU + DTIC + Epi	28	28.5	10	Nr	Bajetta (1998)
Temoz + X	53	34	13.6	35.3	Kulke (2009)
Temoz	12	8	Nr	Nr	Ekeblad (2007)
Temoz + Cape	30	70	18	Nr	Strosberg (2011)
Paclitaxel	10	10	3.2	26	Ansell (2001)
Genitabine	7	0	Nr	11.5	Kulke (2004)
Topotecan	8	0	2.9	26.6	Ansell (2004)

PFS: progression-free survival; OS: overall survival; Nr: not reported; Chloroz: chlorozotocin; FU: fluorouracil; Strepto: streptozotocin; Dox: doxorubicin; CDDP: cisplatin; Temoz: temozolomide; Thalido: thalidomide; Bev: bevacizumab; Ever: everolimus; Epi: epirubicin; X: combination of different drugs; Cape: capecitabine.

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Costa et al Best Pract Res Clin Gastroenterol. 2012

RCTs of cytotoxic chemotherapy for pancreatic NET

	n	ORR	Overall Survival
ECOG[1]			
Streptozocin	42	36%	16.5 months
Streptozocin + 5FU	42	63%	26 months
ECOG[2]			
Streptozocin +5FU	34	45%	16.8 months
Streptozocin + doxorubicin	38	69%	26.4 months
Chlorozotocin	33	30%	18 months
UK NET-01[3] (48% had pancreatic primary)			
Streptozocin + capecitabine	44	24%	26.7 months
Streptozocin + capicitabine + cisplatin	42	36%	27.5 months

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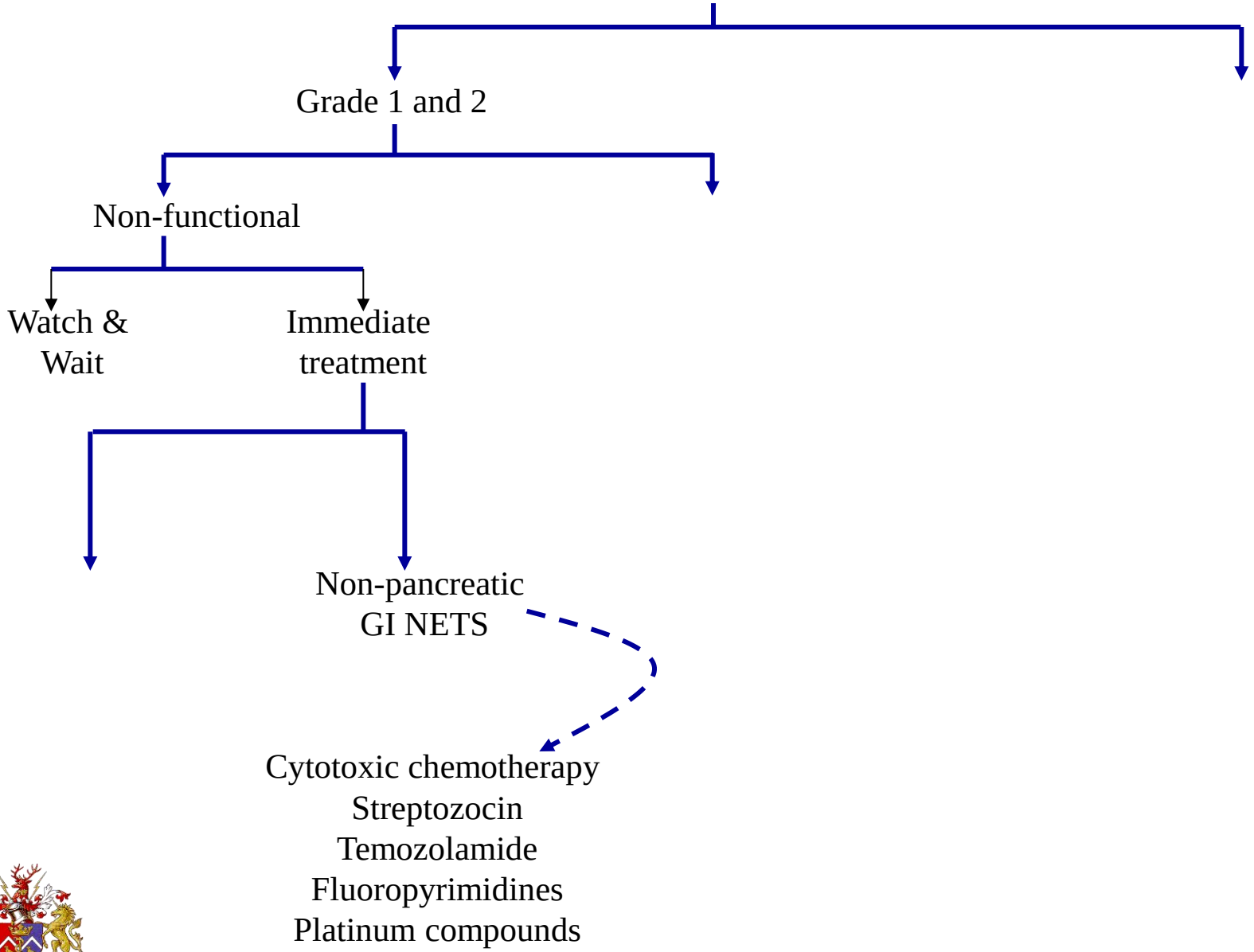
[1]Moertel et al N Engl J Med 1980; [2]Moertel et al N Engl J Med 1992; [3]Meyer et al Eur J Cancer 2014

Systemic therapy for GEP NETs



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Cytotoxic chemotherapy for non-pancreatic GI NET

Regimen	Patients	Objective response (%)	PFS (m)	OS (m)	First author
FU + Strepto	86	22	7.75	16	Engstrom (1984)
Dox	86	21	6.5	12	
FU	19	26	Nr	Nr	Moertel (1979)
CDDP	15	7	Nr	Nr	Moertel (1986)
FU + Strepto	118	33	Nr	Nr	Moertel (1979)
Ciclop + Strepto		26	Nr	Nr	
Strepto	7	3.2	Nr	7.5	Oberg (1987)
FU + Strepto	24	6.4	Nr	18	
Dox + Strepto + INF	11	0	Nr	Nr	Janson (1992)
DTIC	63	16	Nr	20	Bukowski (1994)
FU + Strepto + Ciclop + Dox	56	31	Nr	10.8	Bukowski (1987)
FU + DTIC + Epi	20	10	Nr	Nr	Di Bartolomeo (1995)
FU + DTIC + Epi	12	25	Nr	Nr	Walter (2010)
Temoz + Thalidomide	14	7	Nr	Nr	Kulke (2006)
Gemcitabine	9	0	Nr	Nr	Kulke (2004)
Docetaxel	12	8	Nr	Nr	Kulke (2004)
Paclitaxel	14	7	Nr	Nr	Ansell (2001)
FU + DTIC + Epi	6	17	Nr	Nr	Bajetta (1998)
FU + DTIC	9	11	Nr	Nr	Ollivier (1998)
FU + Strepto	249	16	Nr	24.3	Sun (2005)
FU + Strepto		15.9	Nr	15.7	
Valproic acid	5	12.5	Nr	Nr	Mohammed (2011)

PFS: progression-free survival; OS: overall survival; Nr: not reported; Chloroz: chlorozotocin; FU: fluorouracil; Strepto: streptozotocin; Dox: doxorubicin; Ciclop: ciclophosfamide; CDDP: cisplatin; Temoz: temozolomide; Thalido: thalidomide; Epi: epirubicin.

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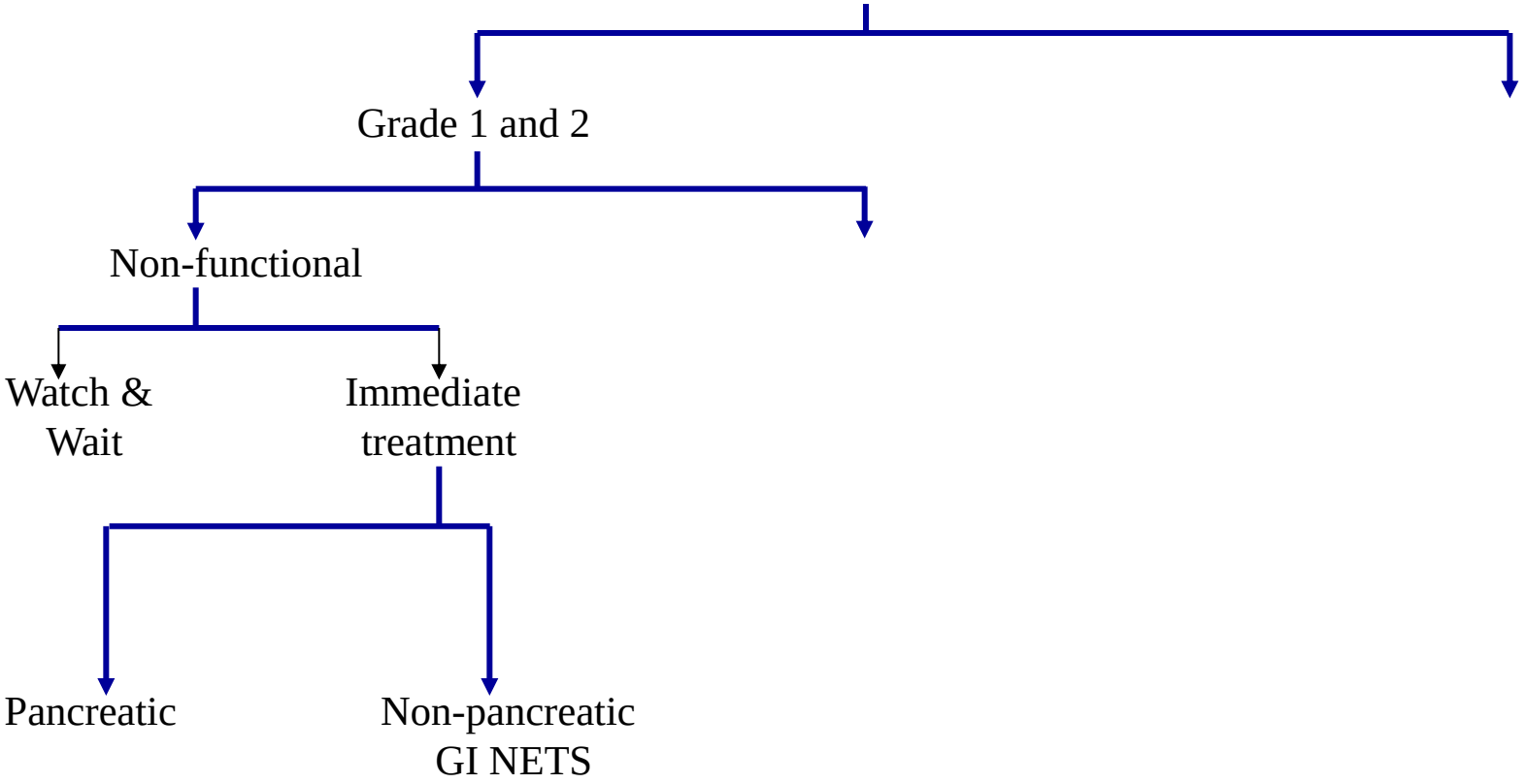
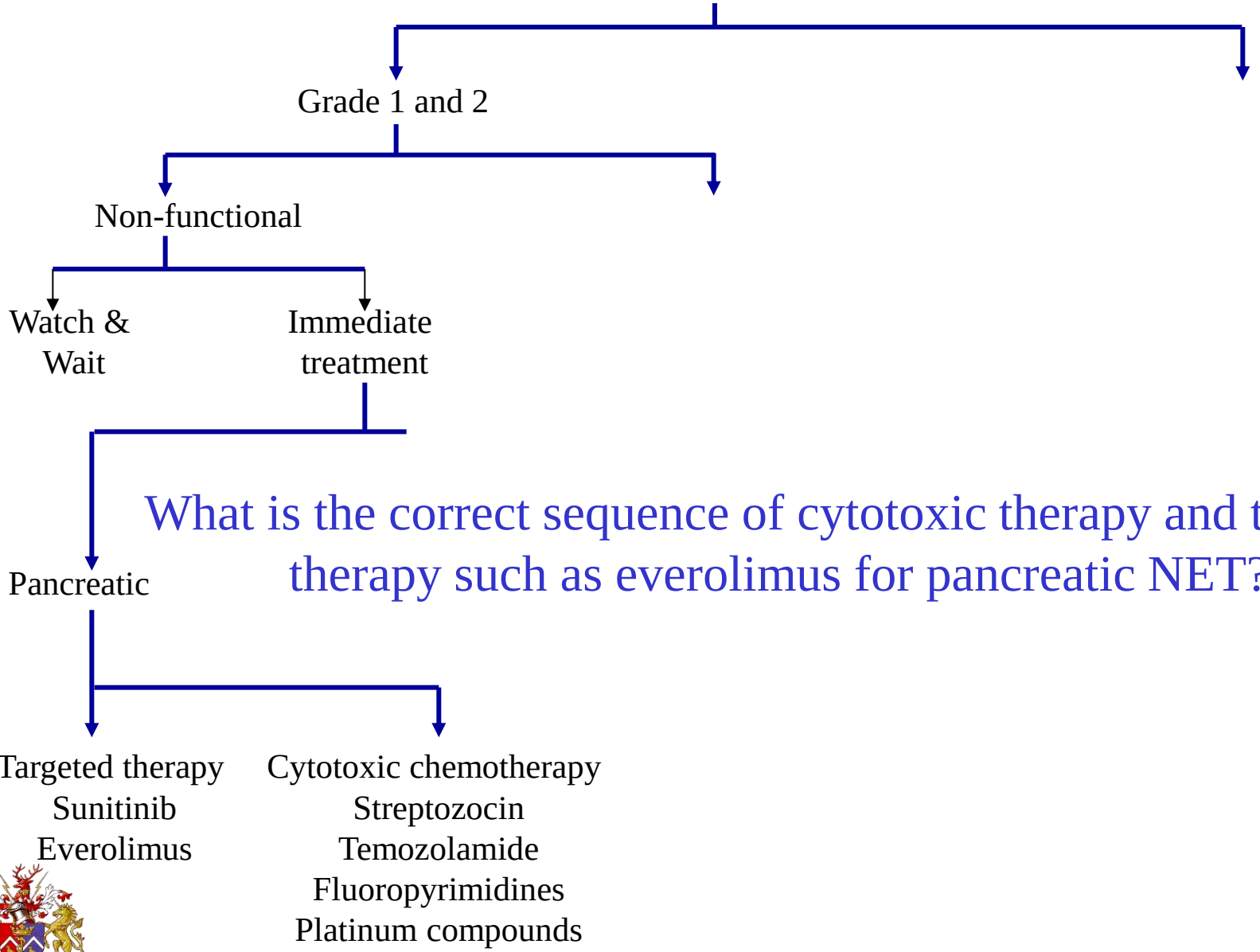
Costa et al Best Pract Res Clin Gastroenterol. 2012

Systemic therapy for GEP NETs



Difference in survival, response to cytotoxic therapy and possibly to targeted therapy such as everolimus (await RADIANT 4)

Systemic therapy for GEP NETs



What is the correct sequence of cytotoxic therapy and targeted therapy such as everolimus for pancreatic NET?

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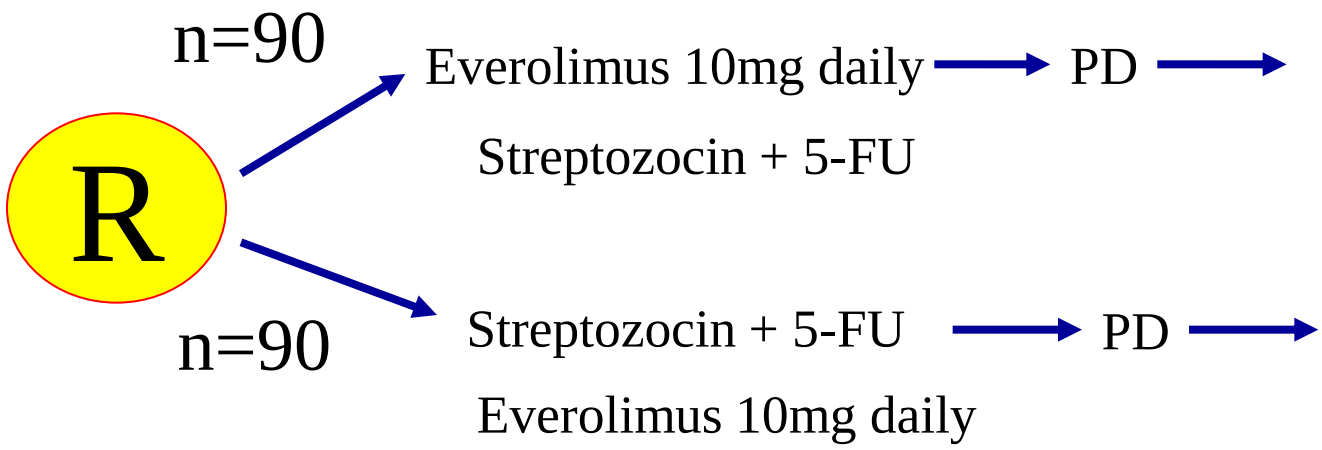
SEQTOR trial design

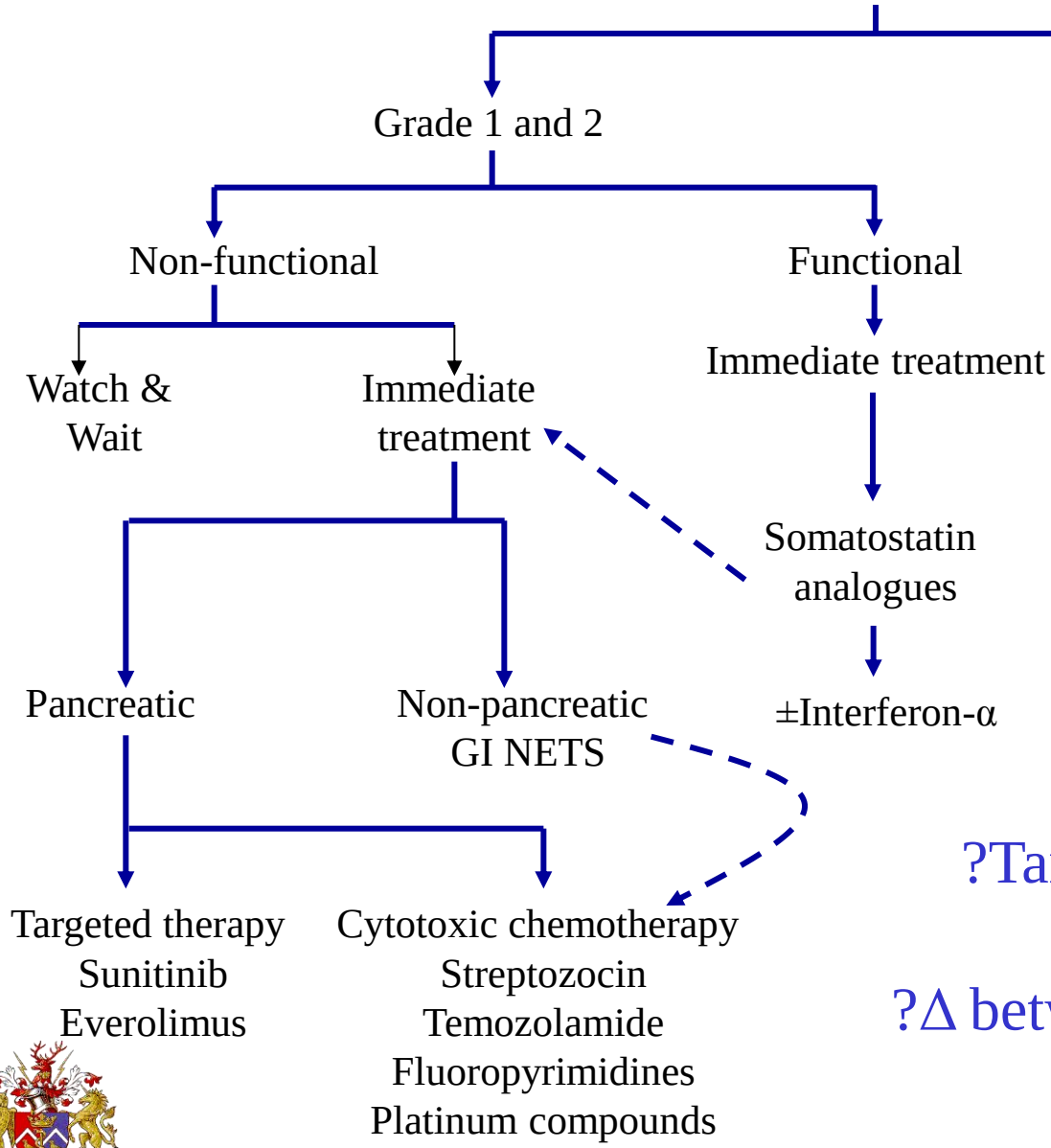
Well or moderately differentiated advanced pancreatic NET with radiological PD within 12 months



Primary endpoint: Second PFS defined as date of randomisation to date of second disease progression

Sample size calculation: to show an improvement for second PFS at 84 weeks from 50% to 75% for the better sequence;
$\alpha = 0.05$, 90% power

Systemic therapy for GEP NETs



?Targeting other molecular pathways

?Δ between pancreatic and small bowel NET

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Commonly mutated genes in pNET vs. PDAC

Genes	PDACs	Pancreatic NETs
KRAS	90+%	0%
TP53	85%	3%
CDKN2A	25%	0%
TGFBR1/SMAD3/SMAD4	38%	0%
MEN1	0%	44%
DAXX/ATRX	0%	43%
mTOR	0.8%	15%

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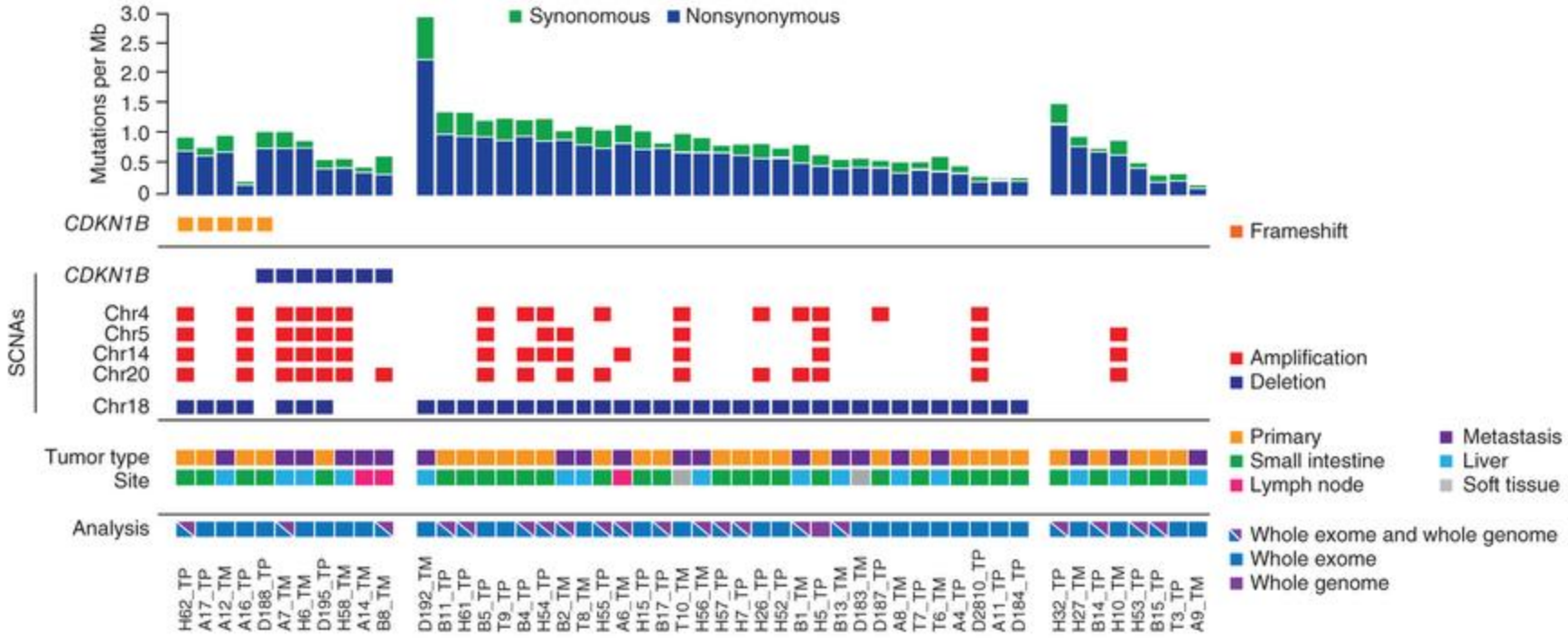
None of these mutations for pNETs are currently targetable for drugs in clinical development

Zhang et al J Natl Cancer Inst 2013

Somatic mutation in small intestine neuroendocrine tumour

- Strikingly few recurrent somatic gene alterations
- Most mutations are likely to be passenger mutations
- CDKN1B mutation has been found in 10% cases and suggest a focus on cell cycle regulation



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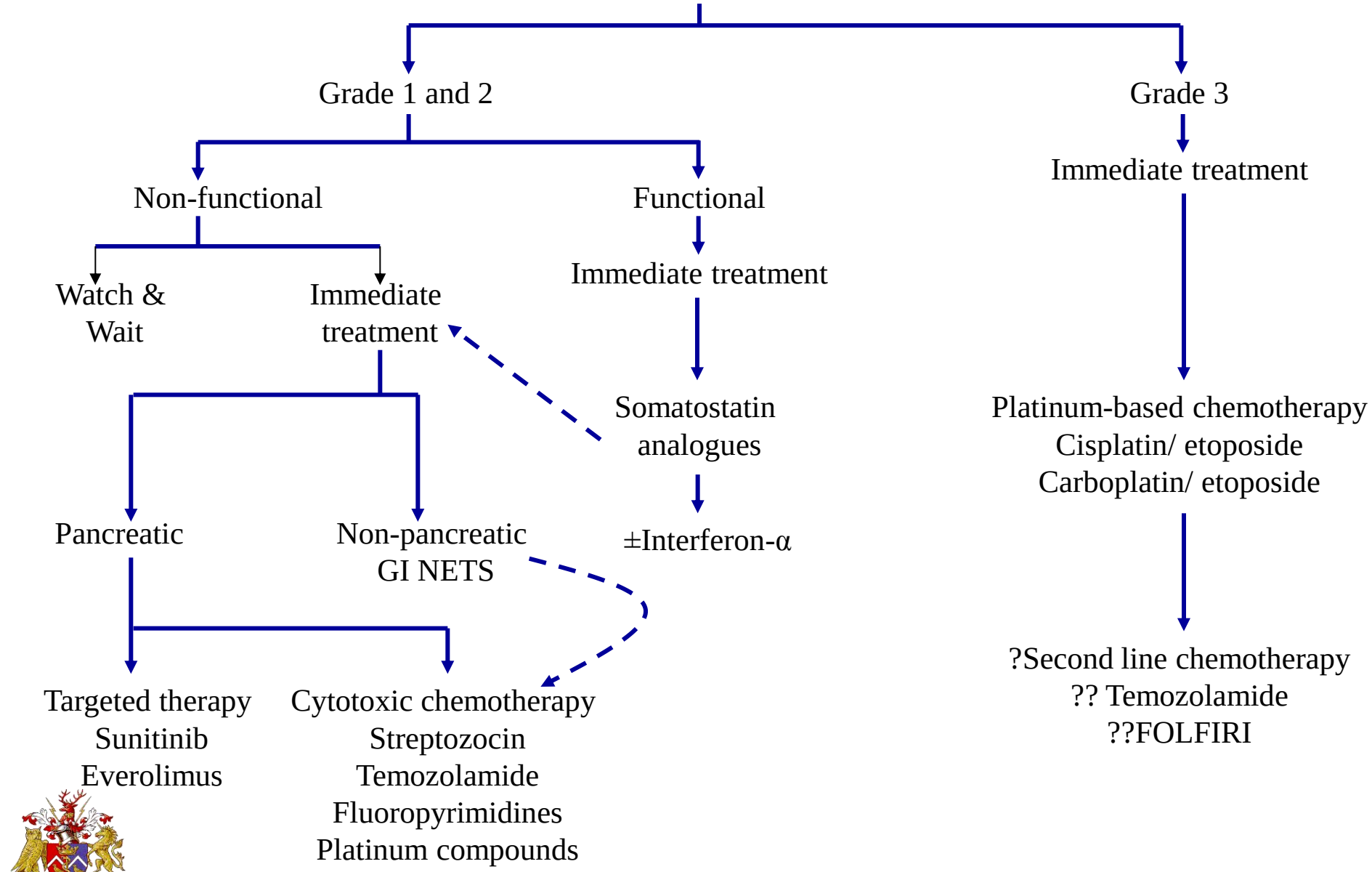
Zhang et al Nat Genet 2013

Systemic therapy for GEP NETs



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